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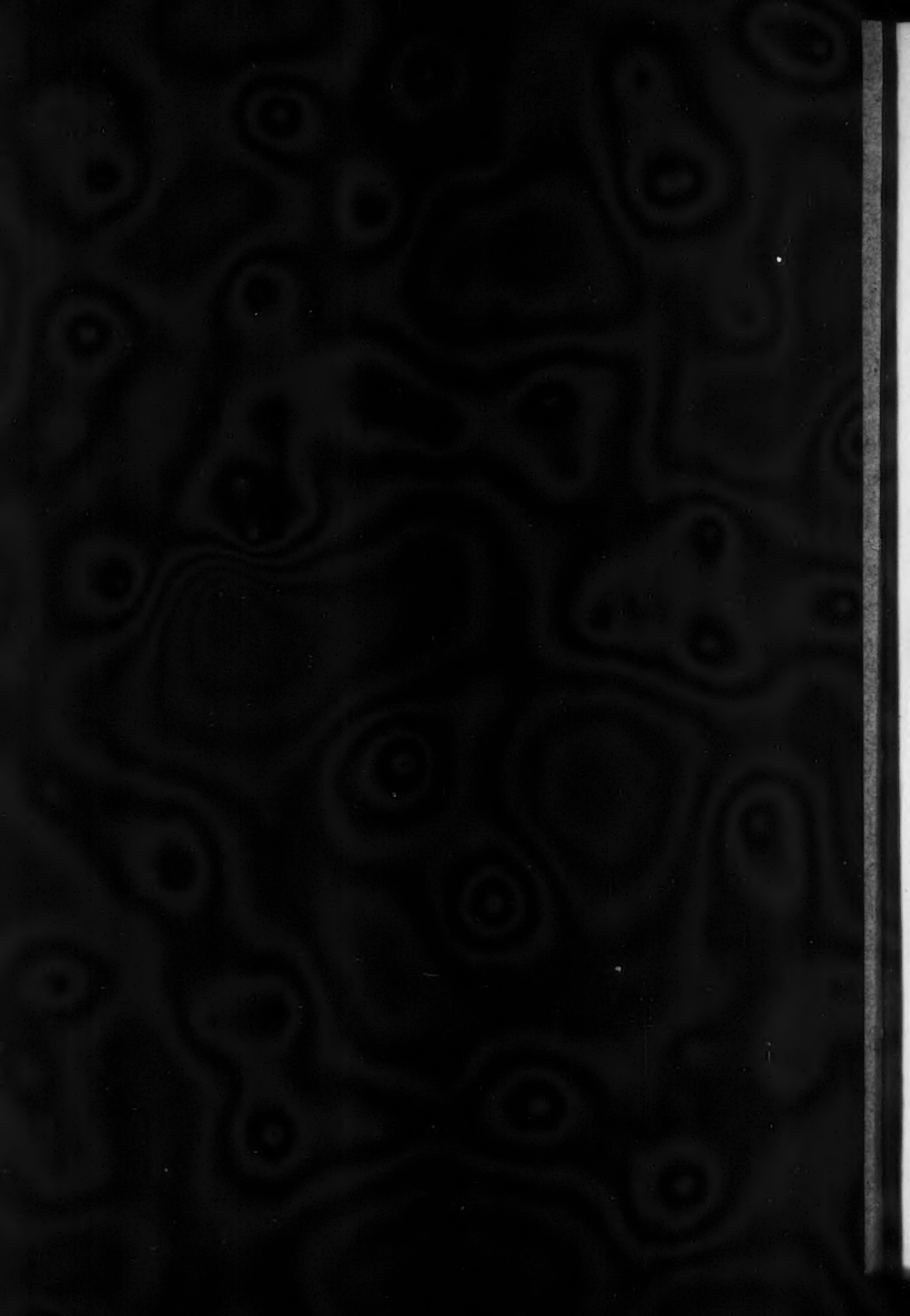

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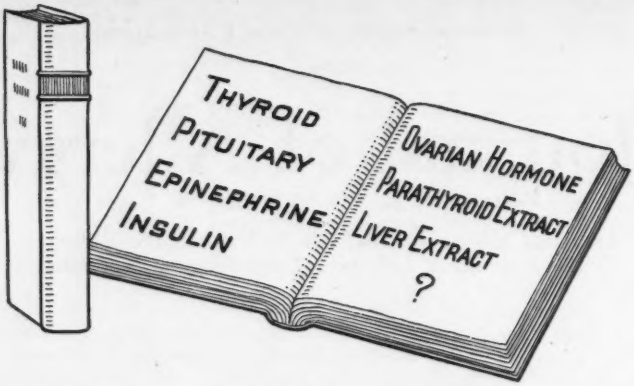

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Volume 13, Number 5 SEPTEMBER-OCTOBER, 1929 Serial No. 67

A FURTHER AND FINAL REPORT ON A CASE OF TETANIA PARATHYREOPRIVA, TREATED FOR A YEAR WITH PARATHYROID EXTRACT (COLLIP), WITH EVENTUAL DEATH AND AUTOPSY*

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SAN FRANCISCO.

INTRODUCTION

Late in 1924, J. B. Collip announced "the extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium." In a series of articles (1, 2, 3, 4), culminating in his Harvey Lecture (5) Collip presented convincing evidence of the potency of the extract. Suffice it to state that a stable and purified principle was obtained which, when injected subcutaneously into experimental animals, produced a rise in the blood serum calcium level, and which in overdosage resulted in an alarming and sometimes fatal hypercalcemia. It was furthermore shown that frequently repeated small doses of this extract are cumulative in action and will eventually raise the blood calcium to dangerous levels (values over 15 mgm.), due to a "pyramiding of the effect of each successive injection upon the preceding one." Hence the importance of accurate and dependable blood calcium determinations to control the dosage, very much as one checks the administration of insulin by blood sugar estimations, and watches the effect of thyroid extract by determinations of the basal metabolic rate. For the experimental proof, and also for an admirable review of the subject of tetany, the reader is referred to the articles alluded to above.

Soon thereafter reports began to appear of the clinical use of this new extract. Collip and Leitch (6) (January, 1925) reported the first case, namely, one of infantile tetany in a girl twenty-two months of age.

Crile (7) in the course of an article on "Surgery of the Glands of Internal Secretion," wrote as follows (July, 1925): "During the past six

*Read at the Thirteenth Annual Session of the Association for the Study of Internal Secretions, Portland, Oregon, July 5, 1929.

weeks we have been using the hormone discovered by Dr. J. B. Collip of Alberta University, and have secured as definite results as he secured with his experimental animals in both acute and chronic cases of tetany. Five acute cases have been treated with relief in every case; relief of symptoms is usually experienced within 20 minutes to one-half hour after the intravenous injection of one cc. of the hormone. In one exceedingly acute case, in which not a single one of the classical symptoms of tetany was lacking, the first dose was followed within twenty minutes by a disappearance of the subjective symptoms. Three doses of 2 cc. each resulted in complete recovery. Among the chronic cases treated relief has been secured in about 85 to 90 per cent." No detailed protocols were given and it is not known whether blood serum calcium determinations were made.

Davidson (8) (August, 1925) reports "a case of adolescent myxedema, accompanied by nephrosis and by tetany of parathyroid origin, treated with thyroid and Collip's parathyroid extract." The patient, a girl aged seventeen years, was carefully observed from January 28, 1925, until her death, July 17, 1925. Exitus was attributed to a severe toxemia of undetermined origin. Post-mortem examination revealed a very small atrophic thyroid gland and no parathyroids in either upper or lower normal positions; two were found in median positions, the left one somewhat atrophied and the right apparently normal. A chart includes percentage of albumin in the urine, several blood cholesterol, blood urea and basal metabolism determinations, and a great many blood serum calcium determinations, together with the daily dose of parathyroid extract.

The authors (9) (September-October, 1925) reported the first detailed record of tetany in a human being resulting from accidental parathyroid extirpation (tetania parathyreopriva), in which Collip's parathyroid extract was used and controlled by blood serum calcium determinations. This paper covered the first five weeks of treatment; because of the favorable effects obtained it was thought advisable to publish immediately so that the medical profession might be informed of the clinical applications of this new hormone. This patient remained under continuous observation until her death, a period slightly over a year. It is this extended study, together with the vicissitudes encountered, the minute examination of the material removed at operation, and the findings at necropsy, which constitute the basis of the present contribution. The conclusions reached in our preliminary report and the data on which they were based will, for the sake of convenience, be referred to later when this patient's narrative is begun.

Shortly after our report (November, 1925) Snell (10) related the story of a woman, aged 54, on whom thyroidectomy had been performed for toxic adenoma, and who three years later (1924) was still suffering from tetany. At that time her blood serum calcium was 4.8 mgm. per 100 cc. Under massive doses of calcium lactate the patient improved, but the blood serum calcium could not be elevated above 6.7 mgm. per 100 cc. In April, 1925,

calcium lactate was discontinued and parathyroid extract (Collip) injected, a total of 5 to 10 cc. being given daily. A prompt rise in the blood serum calcium was noted, and although the average level tended to be higher than under calcium therapy, it again failed to reach a normal level. It was finally found that a normal blood serum calcium level could be maintained by the combined administration of calcium orally and parathyroid extract subcutaneously; the dosage required for this purpose was 14 grams of calcium lactate daily and one cc. of parathyroid extract (Collip) five times daily. Snell concluded: "That calcium lactate administered alone in maximal doses did not produce and maintain a normal level of blood calcium. The same is true of the dosage indicated for parathyroid extract alone. A combined treatment sufficed to attain and maintain a normal blood serum calcium level." The period covered by this latter treatment was about 26 days at the time of Snell's report.

In May, 1926, Hoag and Rivkin recorded the satisfactory effect of Collip's hormone in four cases of infantile tetany. Further reports of its use in this form of tetany have been contributed by Hoag, Rivkin, Weigele and Berliner (12), Sussmann (13), Leitch (14), and Gibson (15).

Lisser, Smith and Shepardson (16) obtained spectacular relief in a very severe case of tetania gravidarum by injections of this extract (the first injection was of 50 units, given intravenously, with relief of the most distressing symptoms within fifteen minutes).

Inasmuch as this paper concerns itself with the use of Collip's parathyroid extract in the treatment of tetany, no reference need be made to its use in sprue or Paget's disease (reports of which are to be found in the literature), or to the paper of Major and Buikstra, "The Effect of Parathyroid Extract and Liver Extract in the Hypertension Produced by Quanidine Compounds," nor to the paper of Cantarow, Coven and Gordon, "Changes in the Chemical and Physical Characteristics of the Blood Following the Administration of Parathyroid Hormone," nor to the report by Mason of its use in chronic nephritis.

Monteith and Cameron (17) observed a patient for six months in whom tetany and hypothyroidism developed following a second thyroidectomy. The hypothyroidism was controlled adequately by desiccated thyroid. The tetany was partially controlled by calcium lactate orally and completely by injections of Collip's extract. Eighty-two days after operation the withdrawal of the extract resulted in the serum calcium falling to its initial low level, but some two months later on calcium lactate alone the blood serum calcium returned to normal. Subsequently, discontinuance of the calcium was followed neither by lowering of the calcium content of the serum nor by clinical symptoms of tetany.

By 1927 and 1928 sufficient time had elapsed since the introduction of Collip's Parathormone for clinical use, to enable several observers to report their experience in cases of parathyroid tetany where this preparation had been employed over periods of several months rather than a few weeks. As

might be expected, results varied according to the severity of the case. Noehren (18), for instance, in a case of tetania parathyreopriva obtained satisfactory results from relatively small doses of Parathormone (20 units daily, and later 10 units daily), very much as we did in our preliminary report (9). After two months he was able to decrease the frequency of Parathormone injections, and after six months had elapsed ½ cc. every twelve days was sufficient to permit the patient (a nurse) to resume active duty.

Hunter (19) published a case of post-operative tetany, the article being accompanied by a good chart, covering a period of three months. He administered 10 units of Parathormone three times daily, increasing to 15 units t. i. d. After 150 units had been given the serum calcium rose to 16.6 mgm. per 100 cc. During this same period thyroid substance was used (a point which will be referred to later in our paper). Results in this case were very satisfactory.

On the other hand, Hjort and Eder (20) report a case of adult tetany following thyroidectomy in which they encountered considerable difficulty with replacement therapy. Their patient was under daily observation for a period of three and one-half months. A calcium rich diet and rest proved unavailing. Large doses of calcium lactate (5 grams every four hours, day and night) were of some benefit, but under this treatment the fluctuations of the serum calcium were too great. Parathyroid extract given parenterally in large doses, 20 to 130 units daily, had little if any favorable influence on the condition. Parathyroid extract administered parenterally in doses of 130 units a day produced a satisfactory reaction in the serum calcium only when supplemented by oral thyroid therapy. Large doses orally, 3 grams daily, of dessicated parathyroid substance (166 times the ordinary dose), failed to influence the serum calcium, even though accompanied by thyroid therapy. They conclude that replacement therapy is not to be relied upon to too great an extent, and that preventive measures, such as autotransplantation of at least one parathyroid gland, may be more dependable. Other reports which might be cited are those of John (21) and Sahlgren (22).

Returning to our original publication in 1925 (9), the patient was a woman, 30 years old, who had been operated upon for a large adenomatous goiter; the mass extended under the sternum and posteriorly behind the trachea; the patient promptly developed tetania parathyreopriva. Thereupon a careful search was undertaken of the goitrous tissue removed, and three separate parathyroid glands were identified; the status of the customary fourth glandule was then unknown. This patient was treated with injections of Collip's parathyroid extract and a detailed account of this treatment, together with its effect on the blood serum calcium, was summarized in a chart and published in the article referred to above. During the first three weeks parathyroid extract alone was administered. We were struck by the fact that subjective improvement was almost immedi-

ately effected by the parathyroid extract, and preceded by several days the objective improvement, as evidenced by the reaction to Chvostek and Trousseau's manoeuvers, and that the relief of both subjective symptoms and objective signs occurred considerably in advance of any marked elevation of the blood calcium. Our report covered the first month of treatment, beginning immediately after the appearance of symptoms of tetany.

In summarizing this initial experience, we were led to the following comment: "It is perhaps premature at this writing to forecast the future of this patient, but it would seem likely that she can be kept free from symptoms and her blood serum calcium maintained at a normal level by the injection of small doses of parathyroid extract combined with calcium lactate by mouth.

"In view of the fact that at least three parathyroid glands were inadvertently removed, it is altogether probable that treatment will have to be continued more or less indefinitely. This is in accordance with the necessity for life-long administration of thyroid extract in pronounced myxedema. If this individual still possesses one parathyroid gland, compensatory hypertrophy may gradually ensue and eventually produce sufficient hormone to maintain a normal blood serum calcium. The authors hope to keep in touch with this patient and render a further report after long-continued observation."

This further report, long delayed, is herewith presented. Our patient was continuously under observation from the onset of symptoms, September 28, 1925, until her death, October 11, 1926. There are appended, for those who wish to study the story in detail, nine tables, which include the daily dosage of Parathormone and (when given) of calcium per os, as well as the blood serum calcium determinations*; the daily dosage of thyroid substance per os (when given); and occasional notes of her clinical status. Throughout this year of treatment a chart was faithfully continued which graphically expressed the three significant factors, namely, the daily Parathormone dosage, the daily calcium dosage, and their effect on the blood serum calcium level. These three factors formed curves which ultimately extended over about 20 feet of graphic chart paper. It was found impossible to reduce this interesting graph to a size suitable for reproduction without rendering it illegible. Significant portions of the chart, however, have been selected for publication and will be referred to later.

To facilitate narration, the year's story of treatment has been divided into eight chapters.

CHAPTER I. (September 28th to October 12th, 1925.)

This period covers the first two weeks following the onset of tetany. During this time therapy was restricted to daily injections of parathyroid extract which varied from 0 to 37.5 units per day (see Chart No. 1). It

*The blood serum calcium was estimated by the Collip modification of the Kramer-Tisdall method.

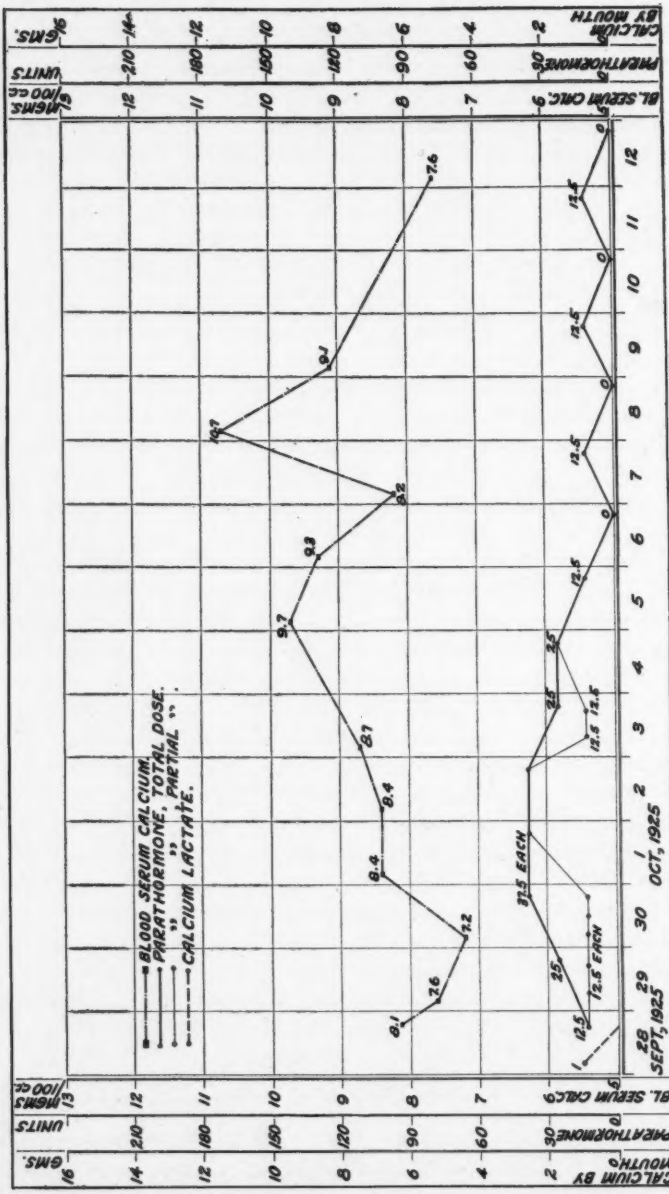
BLOOD SERUM CALCIUM.
PARATHORMONE, TOTAL DOSE.
" " PARTIAL " .
CALCIUM LACTATE.
SEPT, 1925
OCT, 1925
37.5 EACH
25
12.5 EACH
12.5
CALCIUM BY MOUTH
PARATHORMONE
BL. SERUM CALC.
MGMS. /100 cc.
UNITS
GMS.
LISSER & SHEPARDSON

CHART 1

will be noticed that these relatively small doses of Parathormone succeeded in raising the blood serum calcium from 7.2 mgm. per 100 cc. on September 30th, to 9.7 mgm. on October 5th. Fearing a cumulative action from further administration of this potent parathyroid extract, no injection was given on October 6th and only 12.5 units on October 7th. The following day the serum calcium reached a peak of 10.7 mgm. per 100 cc. Consequently, on October 8th, 10th and 12th Parathormone was omitted, while on the intervening days, October 9th and 11th, only 12.5 units were given. The blood serum calcium began to drop immediately, and on October 12th reached 7.6 mgm. per 100 cc.

TABLE I

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1925					
9.28	12.5 u	Lact. 1.0	8.1	None	Symptoms of Tetany.
29	25 u (12.5x2)	None	7.6	"	Comfortable
30	37.5 u (12.5x3)	"	7.2	"	Comfortable.
10.1	37.5 u	"	8.4	"	35 cc. Serosanguinous fluid removed from wound.
2	37.5 u	"	8.4	"	Comfortable.
3	25 u (12.5x2)	"	8.7	"	Comfortable.
4	25 u	"		"	Comfortable.
5	12.5 u	"	9.7	"	Patient ambulatory.
6	None	"	9.3	"	Basal Metabolism 13.8% plus.
7	12.5 u	"	8.2	"	Comfortable.
8	None	"	10.7	"	38 cc. Serosanguinous fluid removed from wound.
9	12.5 u	"	9.1	"	Comfortable.
10	None	"		"	Comfortable.
11	12.5 u	"		"	Queer sensations in body muscles.
12	None	"	7.6	"	Comfortable.
13	25 u	"	7.4	"	Occasional pain in legs and arms.
14	20 u	"		"	Occasional pain in legs and arms.
15	10 u	"		"	Comfortable.
16	25 u (12.5x2)	"	8.1	"	Comfortable.
17	25 u	"		"	Headache.
18	25 u	"		"	Comfortable.
19	50 u (25x2)	"	8.2	"	Comfortable.
20	None	"	10.5	"	Comfortable.
21	"	"	11.9	"	Comfortable.
22	"	"		"	Comfortable.
23	"	Lact. 3.0	8.4	"	Comfortable
24	"	" 3.0		"	Comfortable.
25	"	" 3.0		"	Pain in right arm.
26	"	" 8.0	7.2	"	Pains in both arms—very hungry.
27	"	" 12.0		"	Comfortable.
28	10 u	" 12.0		"	Slight pain in right arm.
29	10 u	" 5.0	8.4	"	Comfortable.
30	None	" 5.0		"	Discharged from hospital.
31	10 u	" 5.0		"	
11/1	None	" 5.0		"	
2	10 u	" 5.0		"	
3	None	" 5.0		"	
4	10 u	" 5.0	8.8	"	
5	None	" 5.0		"	
6	10 u	" 5.0	8.8	"	
7	None	" 5.0		"	
8	10 u	" 5.0		"	
9	10 u	" 5.0		"	
10	10 u	" 5.0		"	
11	10 u	" 5.0		"	
12	10 u	" 5.0		"	
13	10 u	" 5.0	8.7	"	OPD Note: Quite comfortable since discharge.

CHAPTER II. (October 12th to November 4th, 1925.)

During this succeeding period of three and a half weeks (see Chart No. 2), the following interesting events occurred: The blood serum calcium having reached the low level of 7.4 mgm. per 100 cc. on October 13th, daily Parathormone injections were resumed, varying from 10 to 50 units daily, most of the doses being 25 units per day. The last injection of this series was given on October 19th and consisted of 50 units. On this day the blood serum calcium was found to be 8.2 mgm. per 100 cc. Again, fearing a cumulative action of the Parathormone which might send the blood calcium to a dangerously high level, further injections were temporarily discontinued. That this decision was a wise one is borne out by the fact that the preceding seven days' injections, totaling 180 units, resulted in an elevation of the blood serum calcium to 10.5 mgm. on October 20th and 11.9 mgm. on October 21st (despite the fact that no Parathormone was

TABLE II

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1925					
11/14	10 u	Lact. 5.0		None	
15	10 u	" 5.0		"	
16	10 u	" 5.0		"	
17	15 u	" 5.0		"	
18	10 u	" 5.0		"	
19	15 u	" 5.0		"	
20	15 u	" 5.0	8.8	"	Having some cramps. Cold produces "accoucher" hand
21	10 u	" 5.0		"	
22	10 u	" 5.0		"	
23	15 u	" 5.0		"	
24	15 u	" 5.0		"	
25	15 u	" 5.0		"	
26	15 u	" 5.0		"	
27	15 u	" 5.0	8.5	"	
28	15 u	" 5.0		"	
29	15 u	" 5.0		"	
30	15 u	" 5.0		"	
12/1	20 u	" 5.0		"	
2	15 u	" 5.0		"	
3	20 u	" 5.0		"	
4	15 u	" 5.0	8.6	"	OPD Note: Occasional cramp Rt. foot
5	20 u	" 5.0		"	
6	15 u	" 5.0		"	
7	20 u	" 5.0		"	
8	20 u	" 5.0		"	
9	20 u	" 5.0		"	
10	20 u	" 5.0		"	
11	20 u	" 5.0		"	
12	20 u	" 5.0	7.8	"	OPD Note: Occasional minor cramps
13	20 u	" 5.0		"	
14	20 u	" 5.0		"	
15	20 u	" 5.0		"	
16	20 u	" 5.0		"	
17	20 u	" 5.0		"	
18	20 u	Lact. 6.5	8.3	"	Trousseau xxx. Gained 23 pounds since 10-30-25.
19	20 u	" 6.5		"	
20	20 u	" 6.5		"	
21	20 u	" 6.5		"	
22	20 u	" 6.5		"	
23	20 u	" 6.5		"	
24	20 u	" 6.5		"	
25	20 u	" 6.5		"	
26	20 u	" 6.5		"	
27	20 u	" 6.5		"	
28	20 u	" 6.5		"	

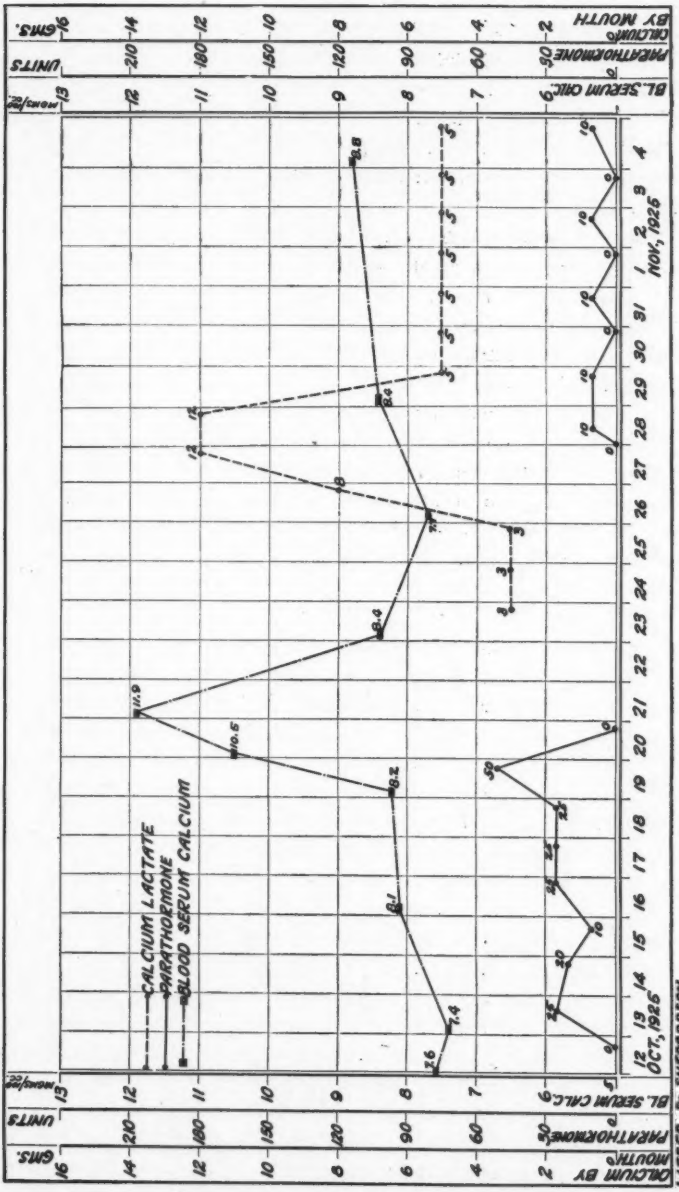
CALCIUM LACTATE
PARATHORMONE
BLOOD SERUM CALCIUM
CALCIUM BY MOUTH
PARATHORMONE
BL. SERUM CALC.
BL. SERUM CALC.
PARATHORMONE CALCIUM BY MOUTH
OCT. 1925
NOV. 1925
LISSER & SHEPARDSON

CHART 2

administered on either October 20th or 21st). However, this high level was not long maintained; by October 23rd it had dropped to 8.4 mgm. per 100 cc. It was then thought advisable to observe the effect of calcium lactate alone (given orally). Three grams were administered on October 23rd and also on the 24th and 25th. Apparently this was without effect on the blood serum calcium, for on the morning of the 26th it had dropped still further to 7.2 mgm. per 100 cc. On October 26th the calcium lactate was increased to 8 grams, and on October 27th she received 12 grams. However, the following day her fasting blood serum calcium was only 8.4 mgm. per 100 cc.

It became evident that it would probably be impossible to force the blood serum calcium to normal by means of oral administration of calcium lactate alone, and in view of the fact that the patient was again having symptoms, such as cramps in her feet and arms, together with some paraesthesias, the calcium lactate was, on October 29th, reduced to 5 grams daily, and 10 units of parathyroid extract was given every other day.

The patient was discharged from the hospital on October 30th, having been carefully instructed in the hypodermic administration of parathyroid extract, of which she was to give herself 10 units every other day. In addition, she was to continue taking calcium lactate by mouth, 5 grams daily in divided doses. Under this regime her blood serum calcium reached 8.8 mgm. per 100 cc. on November 4th.

CHAPTER III. (November 5th, 1925, to January 17th, 1926.)

This period of two and a half months may be likened to a plateau stage. She was at home reporting every week or two to the Ductless Gland Clinic of the Out-Patient Department. If this chapter were charted graphically, it would present a very monotonous picture, and is therefore better studied in the appended tables. For about half of this period the patient took 5 grams daily of calcium lactate orally, and during the latter half 6.5 grams daily. It was soon found that Parathormone had to be administered every day. At first 10 units sufficed, but this soon had to be increased to 15 units, then to 20 units, and finally to 30 units per day. Even with this increased dosage the blood serum calcium was never above 8.8 mgm. per 100 cc., and at one time dropped as low as 7.8 mgm. per 100 cc. Aside from some minor cramps in her hands and feet, the patient was quite comfortable for two and a half months; that is, until January 17th.

It is already apparent, from the foregoing, that the patient's tolerance for the hormone had gradually increased. It will be recalled that at the outset of her illness less than 30 units per day, over a period of one week, was sufficient to raise the blood serum calcium to 11.9 mgm. per 100 cc. This is in striking contrast to the slightly subnormal level of 8 to 9 mgm. per 100 cc. maintained by daily doses of 20 to 30 units over a period of two and a half months (not to mention the additional factor of 5 to 6.5 grams of calcium lactate per day).

CHAPTER IV. (January 17th to February 10th, 1926.)

On January 16th the patient reported to the Clinic; she was decidedly weak, although able to get about. She suffered from transitory paresthesias and a very definite cramping of the thumbs. It was thought advisable to have her under closer scrutiny, and she was therefore again placed in hospital on January 18th. Blood serum calcium on the following morning was 8.2 mgm. per 100 cc. Inasmuch as the patient was restless and complained of smothering sensations, the Parathormone dosage was increased, in the hope of elevating the blood serum calcium, but despite 40 units daily

TABLE III

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1925					
12/29	20 u	Lact. 6.5		None	
30	20 u	" 6.5		"	
31	30 u	" 6.5		"	
1926					
1/1	20 u	" 6.5		"	Felt dizzy—sick—cough—mild bronchitis.
2	30 u	" 6.5		"	
3	20 u	" 6.5		"	
4	30 u	" 6.5		"	
5	20 u	" 6.5	8.1	"	OPD Note: Eye muscles feel stiff Trousseau x.
6	30 u	" 6.5		"	
7	20 u	" 6.5		"	
8	30 u	" 6.5		"	
9	20 u	" 6.5		"	
10	30 u	" 6.5		"	
11	20 u	" 6.5		"	
12	30 u	" 6.5		"	
13	30 u	" 6.5		"	
14	30 u	" 6.5		"	
15	20 u	" 6.5		"	B.M.R. 8.1% plus.
16	30 u	" 6.5		"	OPD Note: Gained 33 pounds since 10–15–25.
17	20 u	" 6.5		"	Occasional parasthesias and cramp of thumb.
18	30 u	" 6.5		"	Re-entered hospital—weak but ambulatory.
19	40 u (20x2)	" 6.5	8.2	"	Restless—smothering feeling.
20	40 u (20x2)	" 1.5		"	
21	40 u (20x2)	" 2.5		"	
22	50 u (20x30)	" 3.0	7.3	"	Pains in arms.
23	100 u (50x2)	" 3.0		"	Restless—silly—some dizziness—insomnia.
24	100 u (50x2)	" 3.0		"	Convulsion — twitching — labored breathing.
25	100 u (30,40,30)	" 3.0	7.7	"	Pains in shoulders and arms. Weight 103.6 kgm.
26	100 u (30,40,30)	" 3.0		"	Twitching of muscles—left shoulder.
27	100 u (30,40,30)	" 3.0		"	Same.
28	None	" 2.0	7.7	"	Same.
29	"	Brom. 3.0		"	Comfortable.
30	"	" 4.0		"	Comfortable.
31	"	" 6.0		"	Comfortable. Weight 100.1 kgm.
2/1	"	" 6.0	9.2	"	Comfortable.
2	"	" 6.0		"	Comfortable.
3	"	" 4.0		"	Ate very little.
4	"	" 4.0		"	Comfortable.
5	"	" 4.0	7.9	"	Comfortable.
6	"	" 6.0		"	Comfortable.
7	"	" 6.0		"	Comfortable. Weight 98.3 kgm.
8	"	" 6.0		"	Ate very little.
9	"	None	8.5	"	Headache—sodium Br. 8.0.
10	"	"		"	Sodium Br. 8/. Ate little.
11	75 u	Brom. 2.0		"	Fever Began. See Fig. IV. Uncooperative.
12	200 u (100x2)	" 3.0	6.7	"	Ate little—skin tender.
13	100 u	" 6.0		"	Muscle spasm—slight chill.

for the next three days the calcium content of the blood serum dropped to 7.3 mgm. per 100 cc. on the morning of January 22nd.

Clinically she appeared worse, and complained of pains in her arms; she was restless, unable to sleep, rather silly in her actions, twitched, and appeared to be on the verge of outspoken tetany. We thereupon, with some trepidation, embarked on more radical Parathormone dosage and injected 500 units in the next five days, an amount we would not have dared to give earlier (see Chart No. 3). We were surprised and disappointed to find that this enormous dosage was without immediate effect as far as her blood serum calcium was concerned, although it resulted in decided clinical improvement.

On January 28th (following five daily doses of 100 units of Parathormone) the blood serum calcium was only 7.7 mgm. per 100 cc. Fearing that the patient had acquired a sort of "fastness" to Parathormone, we discontinued it temporarily and resorted to calcium bromide orally. The latter was started on January 29th in doses of 4 to 6 grams daily. On February 1st the serum calcium reached 9.2 mgm. per 100 cc. In all likelihood this was the delayed cumulative effect of the huge doses of Parathormone administered the latter part of January. This assumption was borne out by the prompt drop in calcium to 7.9 mgm. per 100 cc. on February 5th and 8.5 mgm. per 100 cc. on February 9th. We concluded that the calcium bromide was having little if any influence on the blood calcium level. However, during the period of calcium bromide therapy (January 29th to February 8th, when no Parathormone was administered), the patient was relatively comfortable. It occurred to us that this might be due to the bromide rather than the calcium element. In order to test this, *calcium* was omitted and 8 grams of *sodium* bromide were given on February 9th and again on February 10th. This strategy was promptly abandoned, however, with the appearance of fever on February 11th. Herewith begins a new episode, to be described in the succeeding chapter.

CHAPTER V. (February 11th to February 23rd, 1926.)

In view of what follows, it is important to reiterate that no Parthormone had been administered from January 28th to February 10th, inclusive. On February 11th a febrile period began which lasted from three to four weeks, the maximum temperature never exceeding 38.6° centigrade (see Charts 4 and 5). Not knowing what complications might be developing, and fearing that the fever might have an unfavorable effect on the calcium metabolism, Parathormone injections were immediately resumed on February 11th. On this day 75 units was given. On the following morning, February 12th, the blood serum calcium had dropped to the critical level of 6.7 mgm. per 100 cc. Having in mind the increased tolerance which our patient had acquired for Collip's parathyroid extract, we dared not trifle with ordinary doses, and therefore administered 200 units

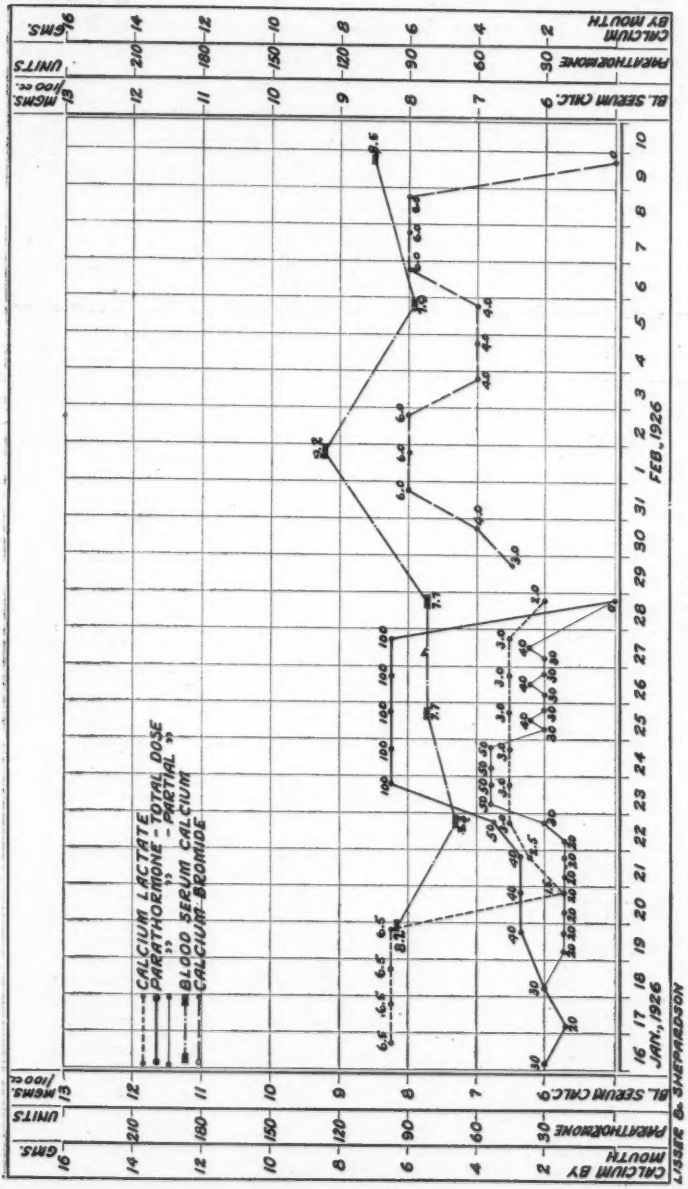
CALCIUM LACTATE
PARATHOREMONE - TOTAL DOSE
" - PARTIAL "
BLOOD SERUM CALCIUM
CALCIUM BROMIDE
JAN., 1926
FEB., 1926
LISSER & SHEPARDSON

CHART 3

within the next 24 hours (see Chart 4). One hundred units was given on February 13th and again on February 14th and 15th. On February 16th 200 units was injected, making a total of 775 units within six days. On the morning of February 17th, blood serum calcium was found to be 8.8 mgm. per 100 cc. Two hundred units more of Parathormone was given on February 17th and again on February 18th. We were disappointed to find that on the morning of the 19th the blood serum calcium had dropped to 7.7 mgm. per 100 cc. Two hundred units more was given on February 19th and 100 units on February 20th, 21st and 22nd. By the morning of

TABLE IV

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926					
2/14	100 u (20x5)	None		None	Trembling of body—having headaches daily.
15	100 u (20x5)	"		"	Fairly comfortable.
16	200 u (50x4)	"		"	Some nausea. Weight 95.8 kgm.
17	200 u (50x4)	"	8.8	"	Fairly comfortable.
18	200 u (50x4)	"		"	Pain in legs, back, arms, very irritable.
19	200 u (50x4)	"	7.7	"	Fairly comfortable.
20	100 u (25x4)	Brom. 4.0		"	Fairly comfortable.
21	100 u (25x4)	" 4.0		"	Twitching—headache—nausea. Wt. 94.7 kgm.
22	100 u (25x4)	" 4.0		"	Trembling—twitching of body and extremities.
23	100 u (25x4)	" 4.0	8.4	"	Headache—restless—chills—thirsty.
24	100 u (25x4)	" 6.0		"	Restless—vomited—alternately hot and cold.
25	100 u (25x4)	" 6.0		"	Vomited.
26	100 u (25x4)	" 6.0	8.6	"	Crying and moaning loudly in night.
27	100 u (25x4)	" 6.0		"	Very irritable—almost frrational—vomited.
28	100 u (25x4)	" 6.0		"	Has been taking only liquids for several days.
3/1	100 u (25x4)	" 6.0		"	Irritable—very noisy.
2	100 u (25x4)	" 6.0		"	Quiet—apparently comfortable.
3	100 u (25x4)	" 6.0	10.4	"	Some solid food.
4	100 u (25x4)	Lact. 4.0		.13	Ate well—irritable—unmanageable.
5	100 u (25x4)	" 6.0		.13	Uncontrollable — unmanageable—severe pain.
6	75 u (25x3)	" 6.0	11.9	.13	Restrained—nauseated.
7	75 u (25x3)	" 6.0		1.3	Quiet.
8	75 u (25x3)	" 6.0		1.3	Restless.
9	50 u (25x2)	" 6.0	12.6	1.3	Fairly comfortable.
10	50 u (25x2)	" 6.0		.13	Vomited—moaning and crying.
11	50 u (25x2)	" 6.0		.13	Moaning.
12	50 u (25x2)	" 6.0		1.3	Headache—otherwise comfortable.
13	50 u (25x2)	" 6.0	10.8	.13	Fairly comfortable.
14	50 u (25x2)	" 6.0		.13	Restless—severe headache.
15	50 u (25x2)	" 6.0		.13	Fairly comfortable.
16	50 u (25x2)	" 6.0	12.0	.13	Moaning—irrational in evening.
17	50 u (25x2)	" 6.0		.13	Restless—ate well.
18	50 u (25x2)	" 6.0		.13	Restless.
19	50 u (25x2)	" 6.0		.13	Pain and restlessness—headache.
20	50 u (25x2)	" 6.0		.13	Restless.
21	50 u (25x2)	" 6.0		.13	Fairly comfortable. Weight 91.3 kgm.
22	50 u (25x2)	" 6.0	12.2	.13	Fairly comfortable.
23	50 u (25x2)	" 6.0		.13	Noisy—restless.
24	50 u (25x2)	" 6.0		.13	Pain in back of neck.
25	50 u (25x2)	" 6.0		13	Comfortable.
26	50 u (25x2)	" 6.0		.13	Some dyspnea.
27	50 u (25x2)	" 6.0		.13	Feeling well—ambulatory.
28	50 u (25x2)	" 6.0		.13	Comfortable.
29	50 u (25x2)	" 6.0	11.6	.13	Some pain in legs.
30	50 u (25x2)	" 6.0		.13	Some dyspnea and palpitation.
31	50 u (25x2)	" 6.0		.13	Comfortable.
4/1	50 u (25x2)	" 6.0		.13	Headache.
2	50 u (25x2)	" 6.0		.13	Comfortable.
3	50 u (25x2)	" 6.0		.13	Comfortable. Weight 89.4 kgm.

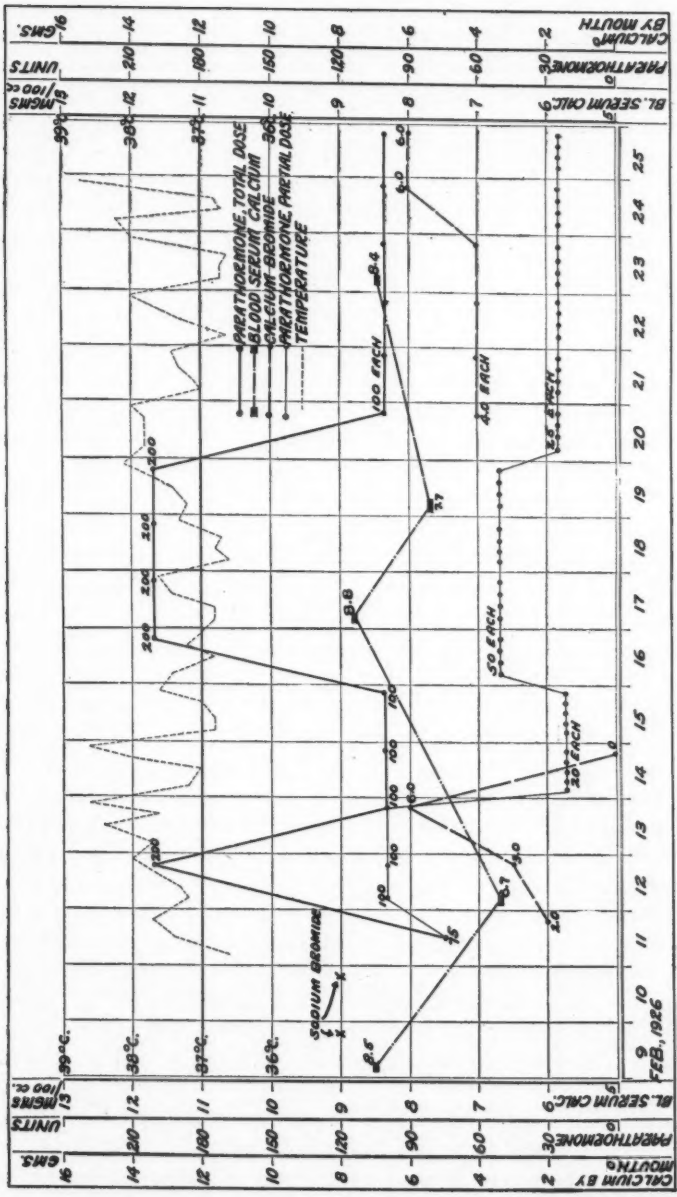
PARATHORMONE, TOTAL DOSE
BLOOD SERUM CALCIUM
CALCIUM BROMIDE
PARATHORMONE, PARTIAL DOSE
TEMPERATURE
SODIUM BROMIDE
100 EACH
50 EACH
25 EACH
10 EACH
FEB., 1926
LISSER & SHEPARDSON

CHART 4

February 23rd the blood serum calcium had increased slightly to 8.4 mgm. per 100 cc.

In summarizing this chapter of twelve days intensive parathyroid therapy, one salient fact looms forth, namely, that 1675 units of Parathormone, an extraordinary amount, had little effect on the blood serum calcium. At the time we were inclined to attribute this to a remarkable increase of tolerance for this preparation. We knew it could not be due to a poor batch of the product, since all of it had been carefully standardized before delivery to us. Subsequent events disclosed that our assumption of increased tolerance was only partly responsible for the weak effect on the blood serum calcium. This will become apparent as the story progresses.

CHAPTER VI. (February 23rd to March 16th, 1926.)

It will be recalled that at the close of the preceding chapter the blood serum calcium level was 8.4 mgm. per 100 cc., and that the patient was receiving 100 units of Parathormone daily (hypodermically) and four grams of calcium bromide orally. A daily dose of 100 units of Parathormone intramuscularly and six grams of calcium bromide orally were continued from February 23rd to March 3rd. By this date the blood serum calcium had finally risen to the normal level of 10.4 mgm. per 100 cc. Calcium lactate was substituted for calcium bromide and 100 units of Parathormone was given on March 3rd, 4th and 5th. The following morning, March 6th, the serum calcium had reached 11.9 mgm. per 100 cc. Wishing to avoid a further rise to possibly dangerous heights, the Parathormone dosage was reduced to 75 units per day; three days later the blood serum calcium reached 12.6 mgm. per 100 cc.; whereupon the parathyroid extract was reduced still further to 50 units per day.

It was probably the subsidence and final disappearance of the fever which enabled us to maintain the blood serum calcium at a satisfactory level on the much smaller dose of 50 units of Parathormone per day. An additional therapeutic factor was introduced about this time, namely, 2 grains daily of dessicated thyroid substance. We were actuated to this procedure by the suspicion that some of the patient's symptoms might be due to a possible hypothyroidism which was masked by the parathyroid deficiency and not demonstrable by basal metabolic rate determinations. It is quite possible that the thyroid extract had a favorable effect of its own on the blood serum calcium and thus permitted smaller doses of Parathormone. We did not introduce it with this objective in mind, but the report of Aub and co-workers (23) confirms the impression we received at that time. In two cases of parathyroid tetany, Aub encountered a similar experience, and he concluded that in tetany due to low blood calcium, thyroid extract raises the blood calcium level as well as increases the calcium excretion. He gave it as his opinion that thyroid substance constitutes a therapeutic adjunct in this disease. However this may be, the combined use of 50 units

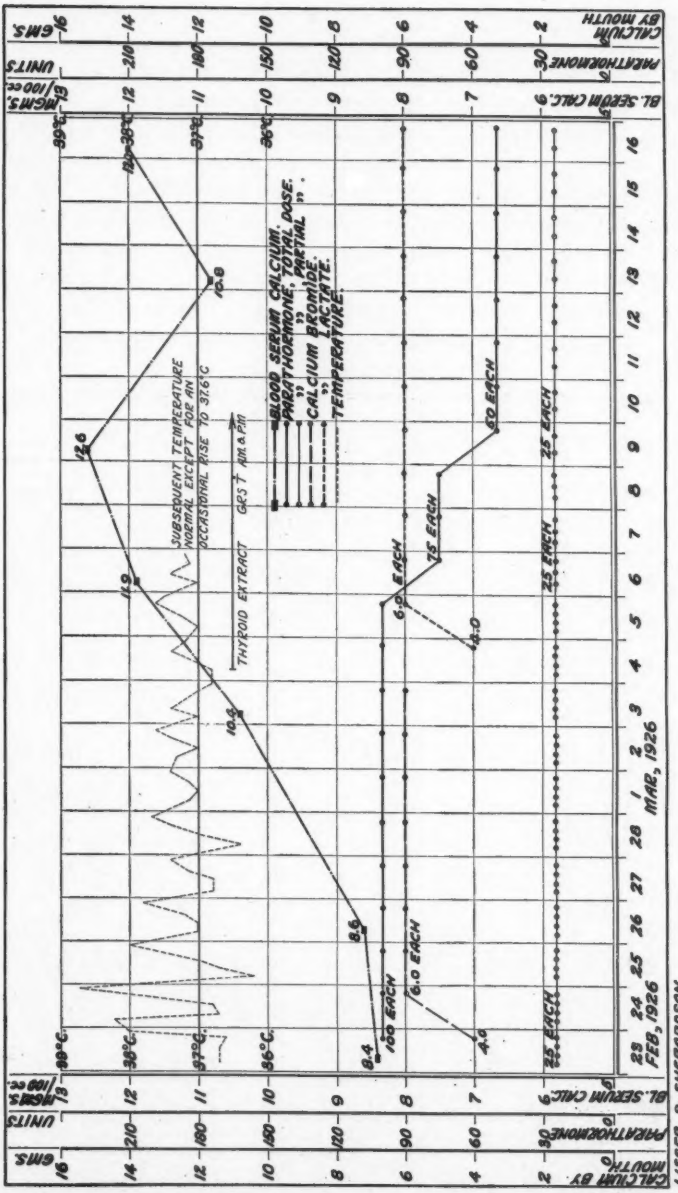
LISSER & SHEPARDSON
BLOOD SERUM CALCIUM.
PARATHORMONE, TOTAL DOSE.
" " PARTIAL " .
CALCIUM BROMIDE.
" LACTATE.
TEMPERATURE.
THYROID EXTRACT GR5 † AM & PM
SUBSEQUENT TEMPERATURE NORMAL EXCEPT FOR AN OCCASIONAL RISE TO 37.6°C
FEB. 1926
MAR. 1926
CALCIUM BY MOUTH
PARATHORMONE
BL. SERUM CALC.
6 EACH
7.5 EACH
10 EACH
12.6
11.9
10.9
10.4
9.6
8.4
6.9
6.0
4.0

CHART 5

of Parathormone, 6 grams of calcium lactate, and 2 grains of dessicated thyroid extract per day, resulted in a blood serum calcium level of 10.8 mgm. per 100 cc. on March 13th and 12 mgm. per 100 cc. on March 16th (see Chart 5).

During the five weeks embraced in Chapters 5 and 6 and graphically portrayed in Charts 4 and 5, little occurred in the patient's clinical status to warrant comment. She was irritable at times, and even irrational and unmanageable; restraint had to be resorted to. Whether this mental excitability was due to the fever or to tetany is difficult to state. Her behavior often suggested hysteria, or possibly a toxic psychosis. The cause of the fever was never explained.

TABLE V

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926					
4/4	50 u (25x2)	Lact. 6.0		.13	Some restlessness—headache.
5	50 u (25x2)	" 6.0		.13	Comfortable—ate well.
6	50 u (25x2)	" 6.0	10.8	.13	Comfortable.
7	50 u (25x2)	" 6.0		.13	Slight nausea.
8	50 u (25x2)	" 6.0		.13	Comfortable—wept in sleep.
9	50 u (25x2)	" 6.0		.13	Comfortable.
10	50 u (25x2)	" 6.0		.13	Comfortable.
11	50 u (25x2)	" 6.0		.13	Screaming with pain in muscles—hysterical.
12	50 u (25x2)	" 6.0		.13	Still has pain in shoulder.
13	50 u (25x2)	" 6.0		.13	Pain all over body.
14	50 u (25x2)	" 6.0		.13	Comfortable.
15	50 u (25x2)	" 6.0		.13	Comfortable.
16	50 u (25x2)	" 6.0		.13	Pain in body.
17	50 u (25x2)	" 6.0		.13	Stupid—drowsy. Not eating well.
18	50 u (25x2)	" 6.0		.13	Comfortable. Weight 90.6 kgm.
19	50 u (25x2)	" 6.0		.13	Comfortbale.
20	50 u (25x2)	" 6.0	10.1	.13	Comfortable.
21	50 u (25x2)	" 6.0		.13	Comfortable.
22	50 u (25x2)	" 6.0		.13	Contracture left hand—opisthotic—cyanotic—hysteria.
23	50 u (25x2)	" 6.0		.13	Restless—see text.
24	50 u (25x2)	" 6.0		.13	Pains all over body. Hysterical.
25	50 u (25x2)	" 6.0		.13	Fairly comfortable. Weight 91.8 kgm.
26	50 u (25x2)	" 6.0		.13	Noisy in sleep.
27	50 u (25x2)	" 6.0		.13	Fairly comfortable—some generalized pain.
28	50 u (25x2)	" 6.0		.13	Nervous—excited—attack of body rigidity.
29	50 u (25x2)	" 6.0		.13	Some pain in shoulder.
30	50 u (25x2)	" 6.0		.13	Comfortable.
5/1	75 u (25x3)	" 6.0		.13	Attack of hysteria. See text.
2	75 u (25x3)	" 6.0		.13	Comfortable. Weight 91.9 kgm.
3	75 u (25x3)	" 6.0	8.8	.13	Severe muscular pains.
4	75 u (25x3)	" 6.0		.13	Comfortable.
5	75 u (25x3)	" 6.0		.13	Comfortable. Not eating well.
6	75 u (25x3)	" 6.0		.13	Comfortable. Not eating well.
7	75 u (25x3)	" 6.0		.13	Attack of hysteria and pain.
8	75 u (25x3)	" 6.0		.13	Comfortable.
9	75 u (25x3)	" 6.0		.13	Comfortable. Weight 92.7 kgm.
10	75 u (25x3)	" 6.0		.13	Parathyroid Implantation.
11	75 u (25x3)	" 6.0	9.3	.13	Parathyroid Implantation.
12	75 u (25x3)	" 6.0		.13	Fairly comfortable.
13	75 u (25x3)	" 6.0		.13	Pain in abdominal muscles.
14	75 u (25x3)	" 6.0		.13	Fairly comfortable.
15	75 u (25x3)	" 6.0		.13	Fairly comfortable.
16	75 u (25x3)	" 6.0		.13	Fairly comfortable.
17	75 u (25x3)	" 6.0	11.6	.13	Fairly comfortable.
18	50 u (25x2)	" 6.0		.13	Fairly comfortable.
19	50 u (25x2)	" 6.0		.13	Fairly comfortable.
20	50 u (25x2)	" 6.0		.13	Fairly comfortable.

CHAPTER VII. (March 16th to September 12th, 1926.)

This lengthy period of six months is condensed into one chapter of our narrative, because it again, like Chapter III, resembled a plateau stage, without extraordinary occurrences. For the first two and half months the patient remained in hospital and was for the most part fairly comfortable, except for occasional outbreaks of an hysterical nature. We could not believe that her emotional excitability was a manifestation of tetany, since her blood serum calcium throughout this time remained fairly high, ranging from 12.2 mgm. per 100 cc. on March 22nd to 8.8 mgm. per 100 cc. on May 3rd, most of the other determinations being above 10 mgm. per 100 cc. (which is average normal).

Realizing that the characteristic effect of Parathormone consists in mobilizing calcium, and fearing that its continuous administration over a

TABLE VI

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926					
5/21	50 u (25x2)	Lact. 6.0		.13	Fairly comfortable.
22	50 u (25x2)	" 6.0	9.2	.13	Fairly comfortable.
23	50 u (25x2)	" 6.0		.13	Fairly comfortable. Weight 91.9 kgm.
24	50 u (25x2)	" 6.0		.13	Some hysteria—slightly irrational.
25	50 u (25x2)	" 6.0		.13	Comfortable.
26	50 u (25x2)	" 6.0		.13	Some hysterical crying.
27	50 u (25x2)	" 6.0		.13	Comfortable.
28	50 u (25x2)	" 6.0		.13	Some nervousness toward evening
29	75 u (25x3)	" 6.0		.13	Comfortable.
30	75 u (25x3)	" 6.0		.13	Comfortable. Weight 93.7 kgm.
31	75 u (25x3)	" 6.0		.13	Comfortable.
6/1	75 u (25x3)	" 6.0	9.2	.13	Comfortable.
2	75 u (25x3)	" 6.0		.13	Discharged from hospital.
3	75 u (25x3)	" 6.0		.13	
4	75 u (25x3)	" 6.0		.13	
5	75 u (25x3)	" 6.0		.13	
6	75 u (25x3)	" 6.0		.13	
7	75 u (25x3)	" 6.0		.13	
8	75 u (25x3)	" 6.0		.13	
9	75 u (25x3)	" 6.0		.13	
10	75 u (25x3)	" 6.0		.13	OPD Note: Feeling fairly well.
11	75 u (25x3)	" 6.0		.13	
12	75 u (25x3)	" 6.0		.13	
13	75 u (25x3)	" 6.0		.13	
14	75 u (25x3)	" 6.0		.13	
15	75 u (25x3)	" 6.0		.13	
16	75 u (25x3)	" 6.0		.13	
17	75 u (25x3)	" 6.0		.13	
18	75 u (25x3)	" 6.0		.13	OPD Note: Has been comfortable.
19	75 u (25x3)	" 6.0		.13	
20	75 u (25x3)	" 6.0		.13	
21	75 u (25x3)	" 6.0		.13	
22	75 u (25x3)	" 6.0		.13	
23	75 u (25x3)	" 6.0		.13	
24	75 u (25x3)	" 6.0		.13	
25	75 u (25x3)	" 6.0	8.1	.13	Notices teeth getting softer.
26	75 u (25x3)	"		.13	
27	75 u (25x3)	" 6.0		.13	
28	75 u (25x3)	" 6.0		.13	
29	75 u (25x3)	" 6.0		.13	
30	75 u (25x3)	" 6.0		.13	
7/1	75 u (25x3)	" 6.0		.13	
2	75 u (25x3)	" 6.0		.13	
3	75 u (25x3)	" 6.0		.13	
4	75 u (25x3)	" 6.0		.13	
5	75 u (25x3)	" 6.0			
6	75 u (25x3)	" 6.0		.13	

period of six months might be depriving the bones of their normal calcium content, x-ray studies of the pelvis and femur were made. No rarification of the osseous structures was revealed. These roentgengrams were taken in April, 1926. In this connection it may mentioned, however, that two months later the patient volunteered the information that her teeth were getting softer.

Seven months had transpired since the onset of her illness, during which time it was necessary continuously to administer increasingly larger doses of Parathormone. There was no end in sight. A recent report (24) of a successful transplantation of a human parathyroid in a case of chronic tetany had come to our attention. Accordingly it was thought advisable to attempt parathyroid transplantation in the hope of achieving a successful graft and thus obviate the necessity for further injections of Parathor-

TABLE VII

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926					
7/7	75 u (25x3)	Lact. 6.0		.13	
8	75 u (25x3)	" 6.0		.13	
9	75 u (25x3)	" 8.0		.13	Chvostek xx. Cramps of eye muscles
10	75 u (25x3)	" 8.0		.13	
11	75 u (25x3)	" 8.0		.13	
12	75 u (25x3)	" 8.0		.13	
13	75 u (25x3)	" 8.0		.13	
14	75 u (25x3)	" 8.0		.13	
15	75 u (25x3)	" 8.0		.13	
16	75 u (25x3)	" 8.0		.19	OPD Note: Better since increasing calcium.
17	75 u (25x3)	" 8.0		.19	
18	75 u (25x3)	" 8.0		.19	
19	75 u (25x3)	" 8.0		.19	
20	75 u (25x3)	" 8.0		.19	
21	75 u (25x3)	" 8.0		.19	
22	75 u (25x3)	" 8.0		.19	
23	75 u (25x3)	" 8.0		.19	OPD Note: Feels and looks fine.
24	75 u (25x3)	" 8.0		.19	
25	75 u (25x3)	" 8.0		.19	
26	75 u (25x3)	" 8.0		.19	
27	75 u (25x3)	" 8.0		.19	
28	75 u (25x3)	" 8.0		.19	
29	75 u (25x3)	" 8.0		.19	
30	75 u (25x3)	" 8.0		.19	
31	75 u (25x3)	" 8.0		.19	
8/1	75 u (25x3)	" 8.0		.19	
2	75 u (25x3)	" 8.0		.19	
3	75 u (25x3)	" 8.0		.19	
4	75 u (25x3)	" 8.0		.19	
5	75 u (25x3)	" 8.0		.19	
6	75 u (25x3)	" 8.0		.19	
7	75 u (25x3)	" 8.0		.19	
8	75 u (25x3)	" 8.0		.19	
9	75 u (25x3)	" 8.0		.19	
10	75 u (25x3)	" 8.0		.19	
11	75 u (25x3)	" 8.0		.19	
12	75 u (25x3)	" 8.0		.19	
13	75 u (25x3)	" 8.0	6.8	.19	OPD Note: Attacks of weakness—apprehension.
14	100 u (25x4)	" 8.0		.19	Entered hospital with tetanic attack. Semistuporous.
15	100 u (25x4)	" 8.0		.19	Discharged from hospital.
16	100 u (25x4)	" 8.0		.19	
17	100 u (25x4)	" 8.0		.19	
18	100 u (25x4)	" 8.0		.19	
19	100 u (25x4)	" 8.0		.19	
20	100 u (25x4)	" 8.0		.19	OPD Note: Feels calm.

mone. Aside from its scientific interest, there was another motive which prompted us to this action, namely, a desire to reduce what might in another patient become a heavy financial burden.* If one studies the appended table, it will be noticed that the blood serum calcium had gradually fallen from 12.2 mgm. per 100 cc. on March 22nd to 8.8 mgm. per 100 cc. on May 3rd. The daily therapy during this time had been the same throughout, except for an increase to 75 units of Parathormone per day two days prior to the relatively low serum calcium level of 8.8 mgm. per 100 cc. (May 3rd).

This increased dosage was decided upon because of one severe and two mild convulsive attacks, characterized by marked painful carpopedal spasms in which both arms and hands were twisted around to the middle of the

TABLE VIII

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926					
8/21	100 u (25x4)	Lact. 8.0		.19	
22	100 u (25x4)	" 8.0		.19	
23	100 u (25x4)	" 8.0		.19	
24	100 u (25x4)	" 8.0		.19	
25	100 u (25x4)	" 8.0		.19	
26	100 u (25x4)	" 8.0		.19	
27	100 u (25x4)	" 8.0	7.2	.19	Chvostek x.
28	100 u (25x4)	" 8.0		.19	
29	100 u (25x4)	" 8.0		.19	
30	100 u (25x4)	" 8.0		.19	
31	100 u (25x4)	" 8.0		.19	
9/1	100 u (25x4)	" 8.0		.19	
2	100 u (25x4)	" 8.0		.19	
3	120 u (30x4)	" 8.0		.19	Chvostek xxx.
4	120 u (30x4)	" 8.0		.19	
5	120 u (30x4)	" 8.0		.19	
6	120 u (30x4)	" 8.0		.19	
7	120 u (30x4)	" 8.0		.19	
8	120 u (30x4)	" 8.0		.19	
9	120 u (30x4)	" 8.0		.19	
10	120 u (30x4)	" 8.0		.19	
11	120 u (30x4)	" 8.0		.19	
12	120 u (30x4)	" 8.0		.19	Entered hospital 9 P. M.
13	50 u (25x2)	" 3.0		.19	Comfortable.
14	100 u (25x4)	" 3.0		.19	Comfortable.
15	75 u (25x3)	" 3.0		.19	Convulsion—See text.
16	105 u (40x2.25)	" 3.0	6.6	.19	Dizzy.
17	160 u (40x4)	" 3.0		.19	Comfortable.
18	160 u (40x4)	" 4.0		.19	Pain in side—convulsions—See text.
19	160 u (40x4)	" 4.0		.19	Comfortable.
20	160 u (40x4)	" 4.0	6.5	None	High fever—See Fig. VI—convulsions
21	160 u (40x4)	" 4.0		"	Vomiting after each meal.
22	160 u (40x4)	" 4.0		"	Vomiting.
23	160 u (40x4)	" 4.0	6.9	"	Nervous—restless.
24	160 u (40x4)	" 4.0		"	Fair day.
25	160 u (40x4)	" 3.0		"	Fair day.
26	160 u (40x4)	" 4.0		"	Restless—eyes feel queer.
27	160 u (40x4)	" 4.0		"	Fair day—occasionally has diplopia.
28	160 u (40x4)	" 3.0		"	Fair day.
29	160 u (40x4)	" 3.0	6.5	"	Fair day.
30	160 u (40x4)	" 4.0		"	Convulsion—See text. Bld. Cult. Neg.
10/1	160 u (40x4)	" 3.0		"	Fair day.
2	80 u (40x2)	" 4.0		"	Pain—numbness of hands—convulsions.
3	25 u	" 4.0		"	2.5 cc. 10% $CaCl_2$ intravenous—two convulsion.
4	160 u (40x4)	" 4.0		"	Abscess on thigh drained yesterday. Comfortable.
5	160 u (40x4)	" 1.0		"	Screaming.
6	160 u (40x4)	" 4.0		"	Several convulsions.

*We were indebted to Dr. Wm. J. Kerr, Professor of Medicine, for a research grant which permitted the free use of a hospital bed together with an ample supply of Parathormone.

back, while the lower extremities were rigidly extended, with toes spread apart. These cramps seemed to be very painful. The peculiar attitude of the arms and hands was the opposite of the characteristic contractions of tetany. We suspected that they might be hysterical.

On May 10th, a parathyroid gland was quickly transferred from a patient undergoing thyroideetomy to the ventral abdominal muscles of our patient. The following morning the blood serum calcium was found to be 9.3 mgm. per 100 cc. This slight rise is better attributed to the recently increased Parathomone dosage (from 50 to 75 units per day) than to the transplanted gland. Another human parathyroid gland was grafted into the body wall on May 11th. On May 17th, six days later, the blood serum calcium had reached 11.6 mgm. per 100 cc. It is possible, though merely a speculation, that this rise of over 2 mgm. per 100 cc. was due to the parathyroid transplants. However this may be, the rise was a transitory one, for the blood serum calcium fell to the former level of 9.2 mgm. per 100 cc. five days later. It is equally possible that the parathyroid transplants had no influence on either the rise or subsequent fall, since it will be noted in the appended tables that the 75 units of Parathormone per day had been reduced to 50 units daily immediately after the blood serum calcium reached 11.6 mgm. per 100 cc.

The patient was discharged from the hospital on June 2nd and was followed in the Ductless Gland Clinic of the Out-Patient Department for the succeeding three and a half months. During this time it was necessary to increase the Parathormone to 75 units per day, and during the last month of this period to 100 units, and finally to 120 units per day. The dose of calcium lactate was also increased from 6 grams to 8 grams per day, and the dessicated thyroid from 2 grains to 3 grains per day. Despite this increased dosage of all three therapeutic constitutents, the blood serum calcium steadily diminished from 11.6 mgm. per 100 cc. on May 17th to 8.1 mgm. per 100 cc. on June 25th, and still further to 6.8 mgm. per 100 cc. on August 13th. It was at this time that the daily Parathormone injections were increased from 75 units to 100 units. This was necessitated not only by the low calcium level, but also by an outspoken attack of tetany, in which the patient was semistuporous and which necessitated three days' hospitalization. During the succeeding month 100 units, and finally 120

TABLE IX

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926					
10/7	160 u (40x4)	Lact. 3.0		None	Convulsion.
8	160 u (40x4)	" 3.0		"	Irrational—several convulsions.
9	160 u (40x4)	" 3.0		"	In coma part of evening.
10	160 u (40x4)	" 3.0		"	In coma all night.
11	None	None		"	Died 12:10 P. M.

units of Parathormone per day was barely sufficient to keep the patient in reasonable comfort. She seemed to be constantly on the brink of tetany. It was, therefore, decided on September 12th to hospitalize her again, for what proved to be the last time.

CHAPTER VIII. (September 12th to October 11th, 1926.)

Three days after entering the hospital the patient developed the first of several epileptiform attacks. They were not Jacksonian in type and certainly not tetanic.

Redlich (25) collected 72 cases in which epilepsy occurred with tetany, 21 being associated with tetania parathyreopriva following strumectomy (as in our case). In this latter group he believed the tetany etiologically responsible for the epilepsy.

Blood serum calcium had reached the critical level of 6.6 mgm. per 100 cc.; consequently Parathormone dosage was again increased, to 160 units per day. This amount was administered daily thereafter for the following 25 days, with the exception of 80 units on October 2nd and 25 units on October 3rd. This dosage was without effect on the blood serum calcium, which remained between 6.5 and 6.9 mgm. per 100 cc.

This inefficacy was in all probability largely due to the occurrence of another febrile episode, for on September 20th the patient's temperature rose rather abruptly to 40° C. The temperature curve can be followed on Chart 6. White blood count on September 20th was 13,350, with 90 per cent polymorphonuclears; 14,900 on September 21st, with 92 per cent polymorphonuclears; and a terminal rise to 34,450, with 90 per cent polymorphonuclears on the day of her death, October 11th. Blood culture on September 30th proved to be negative. On October 4th an abscess in the anterior aspect of the left thigh was incised and 30 cc. of pus withdrawn, culture of which proved to be staphylococcus aureus. This abscess apparently resulted from a self-administered dose of Parathormone given sometime before entering the hospital. Physical examination findings throughout this period were normal, except for this abscess. The patient very likely died of staphylococcus sepsis.

AUTOPSY REPORT*

Complete autopsy was performed, including examination of the bone marrow and examination of the brain and spinal cord. Only positive findings will be mentioned here.

Heart: Weighed 420 grams; coronary arteries were prominent but not tortuous or thickened. The heart was extremely soft, as were all the tissues of the body. There was some slight atheroma about the aortic valves and the coronary orifices, otherwise the ascending aorta was elastic and smooth.

Microscopically, the epicardium was normal. The fasciculi of muscle were moderately uniformly separated but no fibrosis was present. The separation appeared due to a moderate diffuse edema.

*The autopsy was performed by Dr. Leonard Buck and microscopic examinations by Dr. G. Y. Rusk, Professor of Pathology. The writers are indebted to them for the report, excerpts of which are given verbatim.

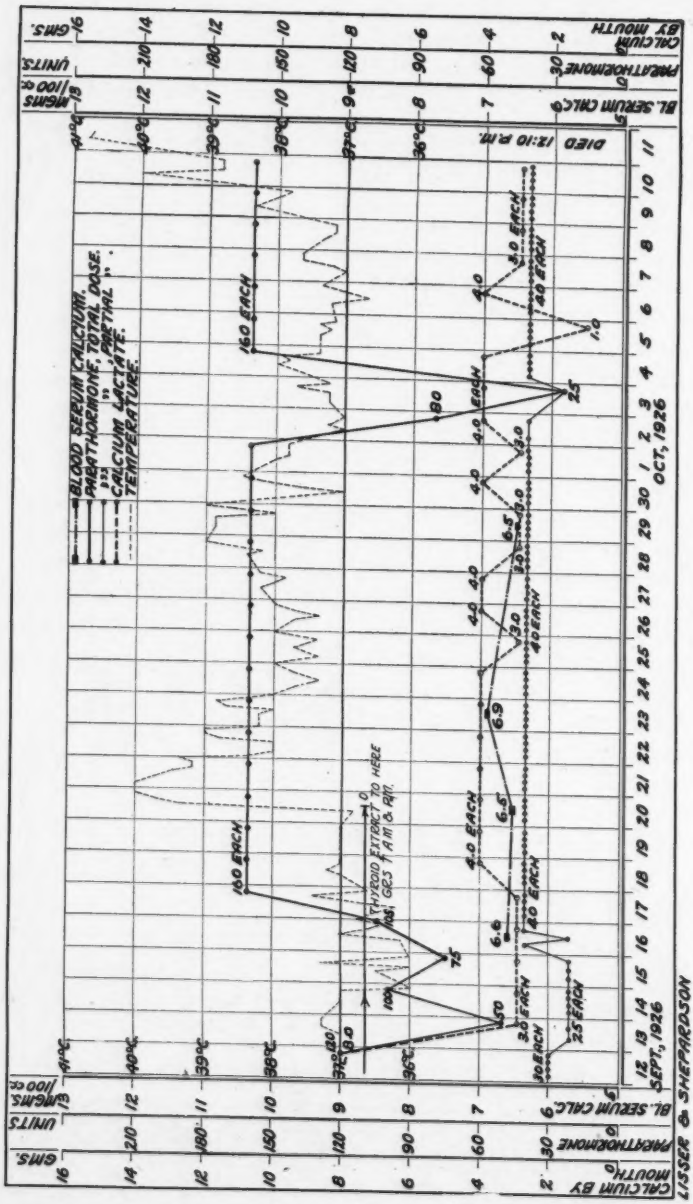
BLOOD SERUM CALCIUM.
PARATHORMONE. TOTAL DOSE.
" " CALCIUM LACTATE. PRETHAL " .
TEMPERATURE.
DIED 12:10 P.M.
160 EACH
100 EACH
4.0 EACH
3.0 EACH
2.5 EACH
1.0 EACH
THYROID EXTRACT TO HERE
OCT., 1926
SEPT., 1926
CALCIUM BY MOUTH
PARATHORMONE
BL. SERUM CALC.
MGMS. /100 c.c.
UNITS
GMS.
LISSER & SHEPARDSON

CHART 6

The gross and microscopical examination of the *lungs* showed a marked edema combined with a moderate diffuse dilatation of the capillaries. In no place was any evidence of inflammatory reaction seen.

The *liver* weighed 1900 grams and was smooth and pinkish-brown. Microscopically, the portal spaces occasionally contained a few lymphocytes. The liver cells showed a finely reticulated cytoplasm. The cells tended to be larger than normal and generally appeared separated and bulbous. This process was seen in cloudy swelling. The sinusoides showed a slight dilatation, otherwise were normal.

The *gall bladder* contained about 30 cc. of light brown bile and 17 pyramidal-shaped gall stones, together weighing 50 grams.

The *spleem* was large, weighing 500 grams. It was 15 cm. in length, 12 cm. in width and 5 cm. in height. Microscopically, the Malpighian bodies varied in size from normal to small. The lymphocytes appeared normal. The arterioles associated with the Malpighian bodies showed hyalin change. The sinusoides in some areas appeared dilated. The pulp elements showed moderate diffuse atrophy with fine diffuse fibrosis.

The *kidneys* were approximately the same size and shape and weighed 440 grams. Microscopically, the capsule appeared normal. The epithelium of the convoluted tubules showed foci of necrosis, also in places the epithelium was eosinophilic where the nuclei were still preserved. Casts occurred in some of the tubules. The interstitial tissue appeared edematous and rarely there was a slight focal increase of interstitial fibrous tissue. Here a few lymphocytes were present.

The gross and microscopic appearance of the *gastro-intestinal tract* was normal, except for some black superficial pigment found in the lower part of the peritoneum, dotted behind the appendix and in the pelvis.

Bone marrow: Microscopically, showed diffuse cellular hyperplasia affecting both the myelocytic elements and the red cells. There were a relatively fairly large number of bone marrow multinucleated cells.

Lymph nodes: Microscopically, sections from various lymph nodes from the abdominal cavity showed general edema. The lymph nodules were indistinct and there was rather marked endothelial hyperplasia.

Brain: The convolutional markings were normal. The leptomeninges and Pacchionian bodies were normal. The basal vessels showed a few very small plaques of atherosclerosis. The covering of the brain was normal. There was a small amount of dark material on the roof of the 4th ventricle. The vessels in the region of the right dentate nucleus were congested with blood. On section of the right cerebral hemisphere there was seen a necrotic-like area in the anterior part of the lenticular nucleus extending throughout its posterior 2/3. The structure in this region was mush-like in consistency. No hemorrhagic staining was seen and it probably was an artifact from poor fixation. There was no reaction about this softening.

THE DUCTLESS GLANDS

The trachea, larynx, and tongue with their surrounding tissue were removed and on section several nodules approximately 1 cm. in diameter were found on the left side of the trachea, which on cut section appeared to be thyroadenoma.

Thyroid: Showed considerable variation in the size of the alveoli. The colloid was unusually abundant. The cells of the thyroid appeared slightly reduced in size. The nuclei stained deeply and the cytoplasm was scanty. Intersecting the glandular elements there were bands of connective tissue. In association with these especially there were small alveoli with little or no evidence of hyperplastic alteration. Areas of diffuse hyalin degeneration occurred; also areas showing the remnants of old interstitial hemorrhage with phagocytic cells bearing pigment. There was a striking lack of the lymphocytic infiltration which accompanies hyperplastic goiters.

Two sections of the abdominal wall were removed under the scars originating from the implantations of *parathyroid* into the recti muscles. Grossly, nothing was seen, except scar tissue and no evidence of parathyroid structure was found microscopically. Careful search failed to reveal parathyroid tissue anywhere in the body.

Thymus: It was an enlarged two-lobed thymus covering the upper part of the pericardium, 1 cm. thick, about 10 cm. wide and 8 cm. long. Microscopically the thymus showed small groups of lymphocytes, appearing rather diffuse as if lying in an edematous background. In these lymphocytic areas there was an additional Hassel corpuscle which appeared quite hyalinized.

Hypophysis: Appeared of normal size. The sinusoides appeared irregularly congested. The glandular portion showed (hematoxylin and eosin stain) the general architecture of the gland to be normal. A very few of the alveoli contained cells which were rather small with scanty cytoplasm. In general the cells were of normal size with neutrophilic cytoplasm, intermingled with which, here and there, were cells, slightly larger in size, showing eosinophilic cytoplasm. Other alveoli were lined entirely with eosinophilic type but the predominating alveolus was lined with the neutrophilic type. There appeared to be a normal proportion between these two types of cells. The pars intermedia showed alveoli lined by cells with smaller darker nuclei, cuboidal in shape, with indefinitely staining cytoplasm. Small accumulations of colloidal material occurred in some of these gland spaces. The amount of pars intermedia appeared normal and no alteration was seen in the structure. The pars nervosa appeared quite normal.

Pineal: Was found to be a smooth, irregular granular-like body 5x3 mm.

Adrenals: The cortex appeared normal. In the center of the gland there was an excessive number of chromatic cells, staining orange color in hematoxylin and eosin. There was also present in the cortex, several more or less circumscribed masses of cortical cells showing marked vacuolation of the cytoplasm due to accumulations of lipoidal material.

Pancreas: Was grossly and microscopically normal.

Uterus: The endometrium showed edema in the more superficial portions. The glands appeared moderately reduced in number. The myometrium was normal.

Ovaries: Showed no noteworthy change.

The Pathologist was impressed by two significant points: First, the complete absence of parathyroid tissue; and, second, by the evidence of intense sepsis. The autopsy was essentially negative in all other respects.

SUMMARY AND COMMENTS

A case of tetania parathyreopriva has been described, in which three parathyroid glands were accidentally removed in the course of strumectomy. Under energetic substitution therapy consisting of increasingly large doses of Parathormone, aided by calcium and thyroid substance orally, this patient was kept alive for one year. Death was probably due to staphylococcus sepsis. Complete autopsy was performed. Careful search failed to reveal any parathyroid tissue.

We were therefore dealing with complete absence of a ductless gland over a period of one year. Inasmuch as neither the clinical course nor the subsequent autopsy findings revealed any noteworthy secondary disturbance in any of the other ductless glands, it would seem reasonable to assume that the parathyroid glandules have very little relation to the other members of the hormonopoietic system. In this respect one is reminded of the disease diabetes mellitus, which, if it be due, as is generally supposed, to a deficiency of the internal secreting portion of the pancreas, is likewise unaccompanied by secondary alterations in the other ductless glands. This is in rather striking contrast to other outspoken uniglandular deficiencies (such as myxedema, eunuchism, and hypophyseal infantilism), or hyperfunctional endocrinopathies (such as exophthalmic goiter, acromegaly and the precocity syndromes due to tumors of the epiphysis cerebri, the adrenal cortex and the gonads), where several glands are eventually involved.

Probably the most significant feature of this year-long treatment with a standardized potent parathyroid extract was the increased tolerance or

immunity which the patient developed toward this product. It became more and more difficult to maintain the blood serum calcium at approximately a normal level, despite the administration of progressively larger doses of Parathormone. In fact, during the last month of the patient's illness 160 units per day failed to raise the serum calcium above 6.9 mgm. per 100 cc. Snell (10) in a recent personal communication mentions an experience in a case of tetania parathyreopriva similar to ours. Hunter (19) includes a personal communication from Aub to the same effect. It would seem that in severe protracted cases of parathyroid deficiency substitution therapy with Collip's hormone, even when combined with liberal doses of calcium, barely suffices to keep the patient alive.

Consequently, when the additional strain of a mild intercurrent infection, which under normal circumstances would be readily withstood, is added, the prognosis is extremely bad. One is at once reminded of the similar condition in diabetes mellitus in which the severity of that disease is markedly increased by mild infections, and just as insulin dosage must then be tremendously increased, so likewise under similar circumstances must Parathormone dosage be augmented. It is interesting, however, that no immunity follows long-continued insulin administration. The increased tolerance which we have stressed in the case of Parathormone may be due to its protein constituent. Possibly a further purification of the extract will eliminate this drawback.

CONCLUSIONS

1. Complete absence of the parathyroid glands for over a year failed to produce any clinical or autopsy evidence of secondary disturbance in the other ductless glands. In this respect, chronic tetania parathyreopriva resembles diabetes mellitus.

2. Although Collip's parathyroid hormone is a biologically standardized product which is promptly beneficial in acute parathyroid tetany, its effectiveness in chronic tetany, where daily injections are necessary for many months, is seriously impaired by an increasing immunity toward the product gradually acquired by the patient. This may be due to an increased tolerance for its protein content.

3. Intercurrent infections in chronic tetany demand augmented Parathormone dosage, just as they do increased insulin dosage when they complicate diabetes mellitus.

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NOTE ON CALCIFICATION IN PITUITARY ADENOMAS

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The differential diagnosis of tumors in the pituitary region, whether they are primarily intrasellar or extrasellar, hinges largely upon the roentgenological features of the case; and the presence or absence of calcification in the lesion has an importance second only to that of the deformations of the pituitary fossa.

Since approximately three out of every four of the tumors that arise from rests of the craniopharyngeal duct show shadows of calcification, the presence of such shadows within or adjacent to the sella is strongly in favor of one of these lesions, particularly if the tumor syndrome has occurred in childhood. It is well know, however, that congential tumors of this nature may remain latent until adult life or middle age at which time new growth of other sorts are more prevalent.

Particular difficulties of diagnosis arise when the chiasmal syndrome of optic atrophy with bitemporal field-defects indicating a local tumor is associated with a sella turcica that is neither enlarged nor deformed. The presence of calcification in the suprasellar tumors that evoke this now well recognized symptom complex whether in children or adults speaks particularly in favor of a craniopharyngeal duct tumor. One, nevertheless, may be misled by shadows of suprasellar calcification that are cast by a psammomatous meningioma, by an aneurysm, by a slowly growing glioma, or even by an adenoma.

Though demonstrable calcification in a pituitary adenoma is rare, it must be taken into consideration in the preoperative diagnosis of the tumors of this important neighborhood, whether they arise within and expand the sella or lie largely above it. It is the purpose of this report to briefly comment upon these cases.

In a review of the roentgenological reports of the 285 verified adenomas in Dr. Cushing's series, it was found that abnormal shadows had been described in some 50 or more instances most of them having unmistakably been cast by residual fragments of eroded clinoid processes or by hyperostoses of the pituitary floor. With the exclusion of all such cases, there remains a group of 19 cases in which the shadows within or just above the pituitary fossa seemed to imply actual calcium deposition within the body of the tumor itself. In this small group of cases there were no constant factors. They compressed seven chromophile adenomas and twelve of chromophobe or mixed types. Ten of the patients were males, nine were females, and the average age was thirty-seven. There was no possible correlation with the probable duration of growth nor with the microscopic

appearance of the lesion. The duration of clinical symptoms varied from one to twenty years.

The site of such calcification cannot be definitely known until suitable necropsies provide an opportunity for examination of the entire tumor specifically for calcification. There were no fatalities in this group of nineteen cases and the calcified area was in no instance identified at operation nor was calcification found on pathological examination of the tissue removed in any case. With but five exceptions the nineteen patients were all operated upon by the transphenoidal route which indicates that the sella was widely expanded and a preoperative diagnosis of adenoma had been made. Usually upon incising the tense dural capsule, soft adenomatous tissue extrudes itself and after a specimen has been taken for verification the larger and softer adenomas have been radically dealt with by suction. By this method of procedure the chances of securing for study the calcified portion of the tumor have been extremely small.

Occasionally in former years patients with an enlarged sella were operated upon by the transphenoidal route for a presumed adenoma and a craniopharyngeal pouch tumor was encountered. Probably all of these cases, in these days of more perfected roentgenography, would have shown calcification. Given a young adult, however, showing such calcification unassociated with enlargement of the sella, a diagnosis of craniopharyngeal pouch cyst is almost inevitable. Even when the sella is expanded one may easily be misled as is shown by the following two examples.

CASE 1. SURG. NO. 18904. CHROMOPHOBE ADENOMA MISTAKEN FOR CRANIOPHARYNGEAL POUCH CYST. TRANSFRONTAL OPERATION. MARKED IMPROVEMENT IN VISION.

Admission: May 26, 1923. Edward D., a student, aged 18, referred by Dr. J. G. Janney of Dodge City, Kansas, with the complaints of headache and failing vision.

Clinical History: Three years before admission the patient began to suffer from generalized headache and bitemporal failure of vision. As headaches became more severe they caused vomiting and were sometimes followed by twenty to thirty hours of deep sleep. For a year and a half he has noticed an increasing thirst and a corresponding increase in urinary output. During the past year he has gained twenty-five pounds in weight and has noticed an undue fullness of the breasts and hips. For the past few months he has had great difficulty in concentration and it is almost impossible for him to keep up with his classes.

Examination: The patient is overnourished and looks about fourteen years of age. The contour of his body and limbs and the distribution of hair is distinctly feminine. The genitalia are normally developed. Of local pressure signs he shows a bilateral primary optic atrophy with bitemporal hemianopsia, V.O.S. 20/100, V.O.D. 20/50. The basal metabolic rate averaged minus eight. Fluid intake and output showed a daily average of 2600 cc. Roentgen-ray examination showed a slightly turricephalic cranial vault. The sella turcica was large and somewhat irregular. There was *a small area of calcification just above the pituitary fossa.*

Considering the age of the patient and the presence of suprasellar calcification, a preoperative diagnosis of craniopharyngeal pouch cyst was made.

Operation: June 9, 1923. The region of the chiasm was exposed by a right transfrontal osteoplastic flap. When the frontal lobe was elevated and the chiasm brought into view, a soft reddish mass was seen projecting up between the optic nerves. After incision of the dural capsule, a large amount of adenomatous tissue was removed and the chiasm and optic nerves freed from pressure.

Postoperative Course: Recovery was uneventful and vision improved rapidly. At the time of discharge, three weeks later, his vision was O.S. 20/50, O.D. 20/20 with normal fields.

Pathology: Sections showed irregular masses of epithelial cells between blood-filled spaces. The epithelial cells were large, with granular cytoplasm and prominent nuclei. No mitotic figures were seen. The cytoplasm was vacuolated and showed no definite granules other than mitochondria. No calcification was seen in the section.

Diagnosis: Chromophobe adenoma.

CASE 2. SURG. NO. 33916. CHROMOPHOBE ADENOMA IN A YOUNG ADULT. MISTAKEN FOR CRANIOPHARYNGEAL POUCH CYST. TRANSFRONTAL OPERATION.

Admission: May 7, 1929. Edward S., a clerk, aged 26, referred by Dr. Frederich Verhoeff of Boston with the complaint of failing vision.

Clinical History: He had always enjoyed perfect health up until one year ago at which time vision began to fail chiefly in the right eye. He was fitted with glasses which served well for about six months. Two months ago in spite of a second change of glasses, he became almost blind in the right eye. There had been no headaches, or other neurological symptoms. He stated that he had always been a little fat and rather overdeveloped about the hips and breasts. Though twenty-six, he needs to shave only once a week. Manifestations of libido have always been very slight.

Examination: Inspection showed a short, somewhat adipose young man. His breasts and hips were rather full, skin smooth and delicate, hair of feminine distribution. All deep reflexes were symmetrically hyperactive. There was an inequality of pupils, the left being the larger. His basal metabolic rate averaged minus eighteen. The local pressure signs found were primary optic atrophy (vision O.D. 20/100, O.S. 20/30) with a temporal hemianopsia in the right eye. Roentgen-ray examination showed the pituitary fossa to be considerably enlarged and expanded. The floor of the sella was depressed and the posterior clinoids were completely eroded. Just medial to the left anterior clinoid was seen a dense curvilinear shadow with multiple fainter shadows posterior to this, strongly *suggesting calcification in the wall of a cyst.*

The diagnosis lay between a craniopharyngeal pouch cyst and a congenital aneurysm.

Operation: May 24, 1929. The chiasmal region was exposed by a right transfrontal osteoplastic flap. On elevating the frontal lobe, the right optic nerve was found frayed out over the bulging pituitary capsule. Upon incision of the dural capsule, soft adenoma began to protrude. The tumor for the most part lay under the right optic nerve pushing this far upward and outward. A sufficient amount of adenomatous tissue was removed by rongeurs and suction to permit collapse of the capsule. At no time was any evidence of calcification met with.

Postoperative Course: The patient made a rapid recovery and was discharged three weeks later. There was, however, no improvement in visual acuity or filling out of his field defect in the right eye, up to the date of discharge.

Pathology: Sections show a very cellular structure consisting of wide bands of closely packed small epithelial cells. There is very little suggestion of architecture and the tissue is quite vascular. The great majority of the cells are of the chromophobe type. Mitotic figures are occasionally found. No calcification was seen in the sections.

Diagnosis: Chromophobe adenoma.

COMMENT

In the first case, an incorrect diagnosis was inevitable. In the second case, though the patient was well below the average age for adenomas, this diagnosis should have been more seriously considered. The roentgenograms of the sella were fairly typical of adenoma in spite of the definite calcification within it.

SUMMARY

Nineteen verified pituitary adenomas have shown shadows of calcification in the roentgenograms. Other cases showing abnormal shadows about the sella have been excluded.

A review of the roentgenograms of these nineteen cases makes it seem fairly certain that the calcification actually lay within the adenoma. All types of adenomas (chromophile, chromophobe and mixed types) were represented in the nineteen cases.

The calcified area was not identified at operation, nor has calcification been detected in a careful review of the bits of tissue that were sectioned. The opportunity of studying an entire gland specifically for calcification was not afforded in this group of cases.*

*It is possible, of course, that an adenoma and a small hypophysial duct tumor may co-exist and the shadows be produced by calcification in the latter lesion. However, since this paper went to press, we have observed calcification in a chromophobe adenoma on microscopical examination of the fresh tissue.

Harvey Cushing

A CASE OF HEBEPHRENIC DEMENTIA PRAECOX WITH MARKED IMPROVEMENT UNDER THYROID TREATMENT*

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In a previous article (1), a summarizing report was made of a series of studies on endocrine factors in dementia praecox. Among 80 patients studied, 14 presented evidence of thyroid deficiency. Of these, nine were diagnosed as definitely and five as probably hypothyroid. Eleven were treated with thyroid substance. In six of the 11, the diagnosis was explicit, and in the other five the evidence of endocrine deficiency was convincing, but the differential findings in some respects were ambiguous. Of the six definitely hypothyroid patients all showed significant mental improvement; four of the five regarded as probably hypothyroid became better. The initial prognosis in each case was unfavorable. Spatial limitations precluded publication of the multitudinous observations involved in the study of each patient. The following case history is presented, therefore, both as an interesting example of striking improvement under medication and as exemplifying the methods used in the research.

The methods are largely those developed by Rowe and his collaborators at the Evans Memorial in Boston (2). In addition to securing as complete family and personal histories as possible and of making careful routine physical examinations, various metabolic studies are made on each patient.

A quantitative analysis of two twenty-four hour samples of urine is made for total solids, total nitrogen, urea nitrogen, uric acid nitrogen, ammonium nitrogen, creatinin nitrogen, and residual nitrogen. In actual practice, the total solids, total nitrogen, and residual nitrogen are the three data of most significance. The ammonium nitrogen gives an index of possible loss of urea through ammoniacal decomposition, and thus casts a light on the dependability of the reported residual nitrogen, which is a derived figure dependent largely for validity on an accurate determination of the urea. In dealing with psychotic patients, there is always an element of uncertainty as to whether an actual twenty-four hour sample is secured. Catheterization as a routine measure is inadvisable because of its unfavorable psychological effect. The creatinin value is therefore of particular

*The cost of this research was defrayed in part by the Memorial Foundation for Neuro-Endocrine Research of Boston.

importance as affording a rough indication of the success in obtaining a true representative specimen. We frequently find it necessary to discard analyses in which the creatinin values fall outside normal limits. The total solids give an indication of the general level of metabolism, and the total nitrogen, of protein metabolism.

Even in a partial twenty-four hour sample, some idea of the level of protein metabolism can be obtained by comparison of the relative proportions of total nitrogen and creatinin nitrogen. We routinely calculate a TN/CN ratio. In the normal subject, with average portein intake, this ratio is about 28. Marked lowering of the ratio is, of course, indicative of protein inanition.

In addition to quantitative analyses, qualitative tests are also made for albumen, reducing substances, and urobilinogen, and microscopic studies are made of the urinary detritus. These may give an indication of serious disturbances of carbohydrate metabolism, of liver dysfunction, and particularly of nephroses or pseudo-nephroses suggestive of thyroid or adrenal deficiency.

As Rowe has emphatically reiterated, this diagnostic system requires the interpretation of each datum in the light of the presence or absence of all factors that may influence it in a quantitative way. Accordingly, the phenolsulphonephthalein output is determined on each patient as an index of the condition of the kidneys, which is potentially able to cause marked displacement of the levels of the various nitrogenous bodies. In short, in the presence of nephritis, the interpretation of the urinary, as well as the blood, chemical findings is quite different than in a case without this complication. Parenthetically, the limitations of the 'phthalein test are recognized.

Basal metabolism is carefully determined in each case. As previously pointed out (3), no little patience is required at times to obtain reliable readings in the case of psychotic subjects. Indeed, occasionally an instance arises in which, for the time being, a satisfactory determination cannot be made. Usually, however, with a few rehearsals, even timorous or recalcitrant patients will relax sufficiently to permit a fairly accurate test. We have various checks on the actual validity of the tests. Ordinarily, with each successive rehearsal, the oxygen consumption is lowered until an approximately constant level is reached. This is likely to be at the true basal level. However, during the course of the determination, both the pulse rate and the respiration rate are determined at brief intervals. In a true basal state, these figures remain essentially constant throughout the test. Any irregularity, therefore, is interpreted as indicating upward displacement from the true basal level. Moreover, the ward attendants record the early morning pulse rates of each patient. A comparison of the ward pulse rate and that obtained during the basal metabolism test obviously indicates whether or not the patient is in a state of actual repose. It is by no means always true that apparently satisfactory relaxation

actually indicates a basal state. The application of these various checks frequently prevents our being led astray by reports from the basal metabolism laboratory. When the first tests are unsatisfactory, repetitions are requested until either convincing evidence of their true basality is secured or it becomes evident that it is not then possible to secure a representative test.

The blood pressure and rectal temperature are routinely determined at each basal metabolism test. The significance of these as criteria of basality would seem to be too obvious to require comment.

Incidentally, these criteria are worthy of widespread adoption. It is no secret that many diagnosticians habitually accept basal metabolic reports at their face value, irrespective of their actual validity. In practice, it is probably true that such reports are as frequently misleading as they are informative. No physician should accept a basal metabolism report that does not include data on both pulse and respiratory rates throughout the period of the tests. He can readily determine for himself the normal rates as well as the blood pressure of his individual patient at rest in familiar surroundings when in a state of genuine repose and use these as criteria. Any report that fails to show constancy of pulse and respiration rates, normal blood pressure and temperature and, especially, a true resting pulse rate, should be disregarded or discounted in accordance with the extent of the vitiating deviations.

The blood morphology is studied in each case. The three data of special endocrine significance are presence or absence and degree of secondary anemia, of lymphocytosis, and of eosinophilia. Secondary anemia is much more characteristic of thyroid than of pituitary deficiency, which conditions may present confusingly similar pictures. Lymphocytosis is likely to be found in any type of endocrinopathy. Eosinophilia points toward pituitary rather than thyroid deficiency.

A chemical analysis of the blood is made for non-protein, urea, uric acid, and creatinin nitrogen, as well as for sugar. Characteristically, the non-protein, as well as the urea nitrogen, is normal in pituitary and ovarian deficiency, but trends upward in thyroid and adrenal deficiency. Uric acid, on the other hand, is typically high in pituitary and adrenal deficiency, but is normal in thyroid and ovarian deficiency. The blood sugar trend is low in adrenal and thyroid deficiency, but normal in pituitary and ovarian deficiency. In our experience, the most useful single datum is high blood uric acid, as differentiating pituitary from thyroid deficiency.

Likewise, especially significant in this regard, is the galactose tolerance. Almost none of the data in Rowe's system are individually pathognomonic. A high galactose tolerance, however, accompanying other signs of glandular deficiency, practically always means pituitary involvement.

The weight, height, trunk length, and chest circumference are determined for each patient. The weight deviations and the sitting-height index

are, of course, well known "constitutional" indicators, and their interpretation needs no special comment in this connection. They have not proved to be of much value in our studies of psychotic patients.

The "lung volume" is determined by the well known spirometer method. A priori, this datum should be of little or no significance, at least in psychotic patients. The amount of air that one is willing to exhale into the instrument would seem to be too much a matter of whim. In actual practice, however, the datum is of considerable importance, especially as an index of thyroid involvement. Shallow respiration is, of course, a well known sign of thyroid disease. In significant degrees of thyroid deficiency, in which the oxygen consumption is materially lowered, the patient seems to establish such a deep seated habit of restricted respiration that his spirometer reading is characteristically affected. Whatever be the explanation, it is an empirical fact that "lung volumes" substantially below prediction are highly indicative of thyroid rather than of other glandular deficiencies. In our practice, the normal volume is calculated to both the Dryer and the West standards, and the average deviation is taken as representing the condition actually present.

Alveolar carbon dioxide is routinely determined for each patient, though we have not been able to convince ourselves as yet that it is a significant datum in psychotic subjects. It is probable that by the use of a method whereby true alveolar air is certainly secured, the determination would be of some significance. It is planned later to introduce such a method.

The foregoing comprise most of the data routinely assembled. The Evans Memorial group have found it expedient to utilize a considerable number of supplementary tests, as determined by special indications in each patient. For the most part, we have not found it practicable to employ such tests in our particular situation. The deterrent factors are partly lack of resources and partly inability to secure adequate cooperation from the patients. In case of the more trying procedure, too, the psychological reactions of the subjects often demand consideration. Schizophrenic patients are prone to delusional misinterpretations and may be made significantly worse by unpleasant and uncomprehended test procedures.

We do, however, systematically make x-ray studies of the sinuses, stomach, and chest, and repeated fluoroscopic examinations for the determination of ptosis or stasis in the colon, and, secondarily, of constipation. Our earlier experiences suggested that liver dysfunction might play a significant rôle in dementia praecox, and for several months we routinely determined the direct and indirect Van den Bergh reactions, the bromsulphalein excretion, and made Graham tests on each patient. The results of the studies (as yet unpublished), however, indicate that liver dysfunction, at least as indicated by these tests, is not an important consideration, and they are no longer included in our routine procedures.

Having assembled the various data, they are first evaluated as to validity. Any demonstrable non-endocrine cause of a given deviation is regarded as vitiating that particular test. For example, eosinophilia in a patient with intestinal parasites has no value as indicating pituitary deficiency. The next procedure is to determine cumulatively the significance of the total mass of evidence. The methods of differential interpretation have been recently set forth by Rowe (4), and need not be reiterated here.

CASE REPORT

The patient, D. S., No. 38,042, an unmarried Armenian factory hand of thirty-four, entered the hospital on January 31, 1928. No significant *family history* is available. The *personal history* is scanty, and was derived through an interpreter from an uncle, whose acquaintance with the patient is not intimate. He was born in Armenia and arrived in the United States about 1913. In 1916 he returned to Europe and was in the French Military Service two years, fighting against the Turks. He then returned to this country and obtained work in Buffalo, New York.

The first manifestations of mental trouble appeared some two years before his admission to the hospital. While working in a restaurant, he complained that voices from the dishes were making trouble for him. An Armenian friend then brought him to Worcester and left him with a cousin. He worked for a short time in a coffee room, then became moody and silent and gave up his position to live with his cousin. He slept badly and would occasionally jump out of bed to explore the room. At times he laughed in a silly manner. He began to eat very sparingly and, if allowed, would stand all day in a corner, staring into space. He then became mute, disoriented, and unable to recall past events. He walked into a lake and called for help. He was afraid of noises.

On admission, physical examination disclosed no significant abnormalities except slight exophthalmos and hyper-active knee jerks. He was polite but appeared to be depressed and abashed by his new surroundings. He was partially oriented for time and place, and stated that he was bothered by noises. On the wards, where he soon fell in with the routine, he spent much of his time standing in one place, staring into space. He often laughed in a peculiar, silly manner. He was fairly cooperative and approximately oriented, but appeared generally depressed and apathetic. He was apprehensive, seclusive, preoccupied, and answered questions in an incoherent and irrelevant manner. He showed no insight, and poor judgment. The staff *diagnosis* was "hebephrenic dementia praecox."

On April 3, 1928, the case was reviewed by Dr. L. B. Hill, who confirmed the diagnosis of hebephrenic dementia praecox and recorded a bad *prognosis*, believing that eventual deterioration would be the patient's lot.

On May 28, 1928, the patient was transferred to the research ward for special study.

A blood Wassermann reaction was negative, and physical examination failed to disclose any significant abnormalities.

From urinalysis the protein intake was found to be at a low maintenance level, the residual nitrogen low normal, the total solids low, and the TN/CN index, 23. The basal metabolism was 79 per cent.* The blood pressure was 106-64; the pulse, 54; the rectal temperature, 97.2°; and the respiratory rate 16-18. Conformity with ward observations as well as consistency of pulse and respiratory rates during the test indicated the validity of the basal rate reported.

The blood was normal as regards formed elements except for well marked secondary anemia. The blood chemical findings were normal, as were the 'phthalein output and the galactose tolerance. The weight closely approximated the calculated normal, but the "vital capacity" was only 76 per cent of the predicted value. A *diagnosis* of thyroid deficiency was recorded.

The findings just discussed are fairly typical of thyroid deficiency. An ideal picture, however, would include increased residual urinary nitro-

*We find it convenient to follow Langfeldt (5) in expressing basal metabolism in absolute percentage of normal, rather than in plus or minus deviations as is the common, awkward practice. Thus, "79%" is the equivalent of "-21%."

gen, and lymphocytosis, as well as slightly lower basal metabolic rate and "vital capacity." Many endocrinologists would expect, too, a certain degree of obesity, but our experience with psychotic patients indicates that in this group obesity is not common in either thyroid or pituitary deficiency. The normality of weight and the moderate depression of the basal rate and lung volume were interpreted as signifying a relatively mild degree of the thyroid deficiency.

On June 23, 1928, thyroid *treatment* was initiated at a level of 6 grains, Burroughs & Wellcome preparation, daily. Subsequent experience in numerous other cases indicates that this dosage was well below a significant level. The dosage was gradually increased until 18 grains daily was reached on October 7.

The first apparent effect was an increase in the psychotic manifestations, and the picture became increasingly that of catatonia rather than hebephrenia. In July, the patient became very stubborn and resistive, talking to himself, and being easily angered. This change can be interpreted as significantly favorable, indicating a renewal of acute concern with inner problems, rather than a passive acceptance of the situation, which is an ominous feature characteristic of hebephrenia. Throughout the summer the patient continued mostly mute, dull appearing, seclusive, and depressed, but amenable to directions and able to do simple work in the cafeteria, until September, when, for a period, he refused to work. Late in the fall he became slightly more approachable.

On October 20, the various routine tests were repeated. They showed slightly more satisfactory protein metabolism, complete correction of the secondary anemia, and the development of mild lymphocytosis, but the findings were otherwise very similar to those noted in June. The thyroid dosage was obviously inadequate.

The dosage was therefore gradually increased until December 14, when a level of 33 grains daily of Armour's preparation was reached.* A repetition of the diagnostic studies showed very moderate improvement of protein metabolism and an increase of the basal metabolic rate to 87 per cent. The blood pressure and temperature were slightly improved to 114/58, and 98.2°, respectively, but the pulse remained essentially unchanged. Secondary anemia was again reported, but this finding is so anomalous, in the light of other experiences (6), as to cast doubt on the accuracy of the determination. The patient had gained slightly in weight, and the lung volume had slightly decreased, though not significantly. The findings otherwise were surprisingly similar to those of October 20.

In November, the first significant evidence of mental improvement begins to appear in the notes of the various observers.† He began to speak spontaneously, to be more sociable and less antagonistic and dejected.

The gradual increase in medication continued to January 26, 1929, when a level of 48 grains of Armour's preparation daily had been reached. The patient showed a surprising failure to react physically. His ward pulse and temperature charts showed no significant changes during this period, and the weight was precisely that of October 6. The obvious suspicion arose that the patient was eluding the vigilance of the ward personnel and not actually ingesting the thyroid that was put into his mouth. We were unable, however, to secure any evidence that such was the case. As a routine measure in all cases at first, and later when there is any doubt of cooperation, the medicaments are placed in the patient's mouth, and he is compelled to swallow several sips of water and then open the mouth for inspection. At this time, we were left with a feeling of uncertainty whether the patient actually had a very high tolerance for thyroid or the ability systematically to deceive an experienced nurse. We have had other experiences indicating that schizophrenic patients often do have a remarkably high tolerance for this substance.

On January 26, 1929, an observation period of one month, without medication, was instituted. This resulted in no detectable shift in the average ward pulse and temperature curves, but was followed by a prompt loss of weight of five pounds, which persisted unchanged throughout the month. Beginning on

*We are indebted to Armour & Company for generous supplies of material.

†Although confirmed by the authors, the testimony upon which this report is based is that of independent observers—a psychiatrist, a psychologist, and a nurse.

February 25, thyroxin by vein, one injection weekly, of 10 mgm. was begun, and carried through with one omission to May 21. The patient promptly reacted by loss of weight, this gradually decreasing from 120 pounds at the beginning to 105 pounds at the end of the period. The pulse and temperature, however, as recorded on the wards, were not perceptibly influenced. As determined by laboratory tests, also, the pulse and temperature, as well as the blood pressure, remained unaffected. The basal metabolism, as shown by these separate tests, promptly came up to normal, where it remained throughout this period, except that on April 2, following an interval of two weeks without medication, it had dropped to 85 per cent. During this period, the patient became more depressed and suspicious, and for a short period had to be tube-fed, though at the end of the period he had again begun to improve somewhat, being more accessible and less depressed. He impressed the observers as having become physically weak, though he was distinctly improved in this respect at the end of the period. Whether the weakness was due to the thyroid or to some undetected condition was not ascertained.

On March 6 the case was reviewed by the Hospital Staff and all but one member judged it to be one of catatonic dementia praecox. One psychiatrist thought that the mood swings shown at this time were more indicative of manic depressive psychosis.

The transformation of a hebephrenic to a catatonic picture might well be interpreted as a favorable development, the latter condition in common experience being the more likely to improve. The fact that sufficient affect had been regained to lead a competent psychiatrist to a diagnosis of manic depressive insanity is, of course, likewise favorable.

On May 27, a series of psychometric tests was attempted. The patient appeared to be willing but unable to comprehend problems. He worked slowly, and without any plans. It took him a long time to answer all questions. He was taciturn and occasionally while working made incomprehensible noises. Under these circumstances, an accurate appraisal was impossible, but the results, as they stood, indicated intelligence of imbecile grade. The mental age by the Stanford-Binet tests was 5 1/12, and the I. Q., 36.

On May 26, the intravenous medication was discontinued, and the oral use of Squibb's thyroxin in dosage of 0.8 mgm., t. i. d., was begun.* The reaction to change of medication was prompt. Within three days the patient was reported as eating better, and becoming more alert at his work. The psychologist reported on June 1: "His attitude has apparently changed; he now tries to listen when he is spoken to; tries to do his part of the work; has quite enlisted the sympathy of the attendant and nurse on the ward; apparently he is putting up a fight to come back." His improvement was rapid. On June 19 he attended a baseball game, where he was interested, laughed, and had a good time. He was personally neater and helpful on the ward to the limit of his ability. He became amenable to re-educational psychotherapy, though he failed to show any definite evidence of insight as to his psychosis. He smiled with seemingly normal affect, and announced his purpose to cooperate with the hospital authorities to get well.

The thyroxin treatment continued unchanged to September 14. During the summer he was in a condition of maintained improvement. He was able to make friends on the ward, though he remained shy of strangers. He occasionally showed a depressed expression, though he was usually complacent. He answered readily when questioned and showed normal animation in facial expression. He was well oriented, and no evidence of hallucinations or delusions could be elicited. He became keenly interested in getting out of the hospital and going to work.

On August 7-8, the psychometric tests were repeated. The patient now showed fair cooperation, but was handicapped by language difficulty. His I. Q. was estimated at 55, as compared with 36 in May.

On August 13, his protein metabolism was fairly satisfactory, the protein intake being 60-65 grams. The basal metabolic rate was recorded as 86 per cent, but the blood pressure, pulse, and temperature remained as low as at the beginning. There was still a slight secondary anemia, and the lung volume was 22 per cent below prediction. Blood chemistry, 'phthalein output, and galactose tolerance were normal, but he remained 10 per cent underweight. The findings

*A trial lot of a preparation manufactured by a new method by E. R. Squibb & Sons was employed. We wish to record our appreciation of the cooperation of this firm in supplying the drug.

were interpreted as indicating still some degree of thyroid or other glandular deficiency.

On September 14, the thyroid dosage was increased by the addition of 2 grains of Armour's preparation t. i. d., but the patient was discharged on trial visit on September 23, and the results of the increase were not determined.

At the time of his discharge he was still showing some tendency at times to depression, but was otherwise free of gross psychotic manifestations. It was the opinion of the psychiatrist who last examined him that he was not entirely well.

In view of the failure to secure complete normalizing of metabolism and of the ignorance, low mentality, and relatively friendless position of the patient, it is not unlikely that he will suffer a relapse and return to the hospital for further treatment, though if proper medical supervision with continuation of thyroid medication can be secured, the outcome may be entirely satisfactory.

We are not disposed to attempt any appraisal of the general significance of this report. The final determination of the significance of endocrine factors in dementia praecox must be determined statistically and with a much larger mass of evidence than is now available. While the case reported is by no means unique in our experience, it is, after all, a single case, and examples of unexpected improvement in dementia praecox are by no means rare. The outcome, at any rate, is strikingly better than was to have been anticipated under ordinary hospital treatment.

SUMMARY

The case is reported of an Armenian factory hand of 34, who had been suffering for at least two years of hebephrenic dementia praecox. The onset had been insidious, and a prognosis of further deterioration had been confidently made. He showed no significant gross physical abnormalities, but his protein metabolism was unsatisfactory, his pulse, blood pressure, temperature, basal metabolic rate, erythrocyte count, and "vital capacity" were low. The blood chemistry, galactose tolerance, and weight were normal. His case was diagnosed as one of thyroid deficiency. Under thyroid medication, the psychotic picture became more nearly that of catatonia, then strikingly improved toward normality. Repeated metabolic studies showed that the glandular deficiency was only partially corrected, but the improvement reached a stage justifying discharge from the hospital on trial visit. The case is reported as exemplifying results secured in several other instances.

Our thanks for cooperation are due to numerous fellow workers in the hospital, but especially to Superintendent W. A. Bryan, Dr. M. Yorshis, Mr. A. P. Gulles, Dr. D. A. Shakow, and Miss Anna Walsh.

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A STUDY OF BLOOD SUGAR CURVES BEFORE AND AFTER THYROIDECTOMY*

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The purpose of this paper is to present some interesting blood sugar curves taken before and after thyroidectomy and to study the changes in metabolism incident to surgery, particularly in respect to their bearing on the etiology of diabetes. During the past six years it has been our privilege to study the glycosuria and hyperglycemia occurring in a large number of patients presenting themselves for treatment because of symptoms of hyperthyroidism. In addition we have studied a smaller number of patients who came to us because of symptoms of diabetes but who also presented evidence of hyperthyroidism. In the first group a diagnosis of diabetes was made in a few instances and it is chiefly with these that we are concerned in this paper.

Space will not permit a review of the voluminous literature relative to the combined problem of diabetes and hyperthyroidism. Furthermore, a very complete review was made by John (1) in 1927 and by Lahey and Joslin (2) in 1928. Two previous reviews, one by Fitz (3) in 1921, and later, one by Wilder (4) are also outstanding.

Considerable variance in opinion apparently exists as to what constitutes true diabetes in the presence of hyperthyroidism. Both Fitz and Wilder were extremely cautious not to include any cases in their series wherein there was any doubt as to the presence of diabetes. Joslin and Lahey discarded from their report eleven cases ordinarily classified as diabetes and omitted nine more which they classified as potential diabetes. Their basis for doing so they clearly state: "For the present, therefore, and to avoid premature diabetic cures, we have raised the standard for the diagnosis of diabetes in hyperthyroidism to a blood sugar of 150 mgm. fasting or 200 mgm. or more after meals in addition to glycosuria." They felt that Wilder and Fitz must have used the same diagnostic standards, although this the latter did not specifically state.

Joslin and Lahey consider that hyperthyroidism alone is the factor in disease of the thyroid which leads to glycosuria and is distinctly more important than the accompanying increased metabolism, whereas Wilder states his position as follows: "The phenomena exhibited by patients with true diabetes combined with states of hyperthyroidism or hypothyroidism appear to be related to the general metabolic rate and are therefore susceptible of explanation without recourse to speculation as to a specific

*Read at the Thirteenth Annual Meeting of the Association for the Study of Internal Secretions, Portland, Ore., July 9, 1929.

interdependence of the thyroid and pancreas." John, on the other hand, states that the hyperglycemia and glycosuria associated with hyperthyroidism must be regarded as a functional diabetes with a definite disturbance of the insulogenic apparatus and presents evidence from which he concludes that the degree of hyperglycemia bears no relation to the severity of the hyperthyroidism or to the height of the basal rate.

A fundamental piece of work by Sanger (5) in 1922, in which he studied the respiratory quotient in patients with hyperthyroidism and in controls, led him to conclude that the increase in the respiratory quotient after giving glucose proves that individuals with a thyrotoxicosis burn carbohydrates more readily than normal individuals and inasmuch as their blood sugars remain elevated they obviously cannot be storing it. Thyroid fed animals after a certain period of time have very little liver glycogen even though they are fed on high carbohydrate diets.

We have, therefore, in hyperthyroidism, a liver poor in glycogen because of the insistent calls of the muscles for more glycogen because of the increased metabolism. A similar condition exists in diabetes mellitus, a liver low in glycogen, but for another reason, insufficient insulin to enable the liver and muscles to store it. Macleod (6), commenting on the work of Porges and Salomon, in which they determined the respiratory quotient in dogs in which the pancreas had been removed two days previous to the tying of the vessels of the liver, and found quotients ranging from 0.859 to 1.19, remarks that the chief interest of these results is to show that similar changes in R. Q. occur in completely diabetic animals as in normal ones, and when the influence of the abdominal viscera is removed, thus indicating, contrary to the belief of many, that the muscles in diabetes have not lost their power to oxidize carbohydrate. Joslin (7) states that it is becoming more and more evident that it is not so much the lack of the diabetic to utilize carbohydrate as lack of carbohydrate to utilize.

Hyperglycemia is characteristic of diabetes, whereas by no means is it always present in states of hyperthyroidism, as many patients with severe forms of thyrotoxicosis and high metabolic rates exhibit normal blood sugar curves. In patients, therefore, with hyperthyroidism in which hyperglycemia is present, it must be assumed, in order to explain the anomaly, that some disturbance of the insulogenic apparatus must be taking place. Neither Wilder's explanation, that in hyperthyroidism insulin is more rapidly destroyed, nor Sanger's, that toxic changes in the liver cells prevent storage, is satisfactory, else the hyperglycemia would bear a quantitative relationship to the hyperthyroidism.

Let us now consider the opinions of various authorities concerning the diabetic Anlage according to Naunyn's conception. Joslin (1) raises the question as to whether true diabetes ever occurs in hyperthyroidism unless this factor is present and says that one can hardly fail to reach the conclusion that if the diabetic Anlage were present to only a slight degree in

a patient, hyperthyroidism would bring it to the fore. John (8) quotes Naunyn as follows: "I consider it justifiable to draw the conclusion that the thyroid causes glycosuria only when there exists a predisposition to diabetes." And Von Noorden: "Pure hyperthyroidism in the presence of a fully normal chromaffin system will seldom produce an alimentary and spontaneous transitory glycosuria." Wilder (4) expresses himself in this way: "Patients with no diabetes and consequently with large supplies of insulin, reveal no lack of tolerance for carbohydrates, even when their metabolism is stimulated by extreme grades of hyperthyroidism because their supply of insulin is more than adequate." From this statement it might be implied that an abnormal blood sugar curve in the presence of hyperthyroidism suggests a potential diabetes. According to Joslin's statistics, an hereditary history of diabetes can be obtained in only about 25 per cent of diabetic patients. In his cases of hyperthyroidism and diabetes it was 20 per cent. Statistics are always open to question, despite the care with which they are taken, and are notably unreliable. Moreover, as pointed out by Joslin, the diabetic age zone is around 50 years. It is certainly possible that many potential diabetics may well die of other causes before reaching this age, or, having attained this age, an exciting cause of sufficient force may never have presented itself.

The efficiency of a blood sugar curve as a means of detecting a very mild potential diabetes, it has seemed to us, is open to question from the following point of view. May it not be that a diabetic Anlage of such a mild form may be present as to evade detection by our ordinary methods and be brought out into the open only by the development of hyperthyroidism in the patient? The blood sugar curves of two patients with mild diabetes uncomplicated by hyperthyroidism lends support to this contention (Charts 8 and 9).

In our group of true diabetes and hyperthyroidism there are twenty-four patients who were operated upon. Ten of these were of the parenchymatous and fourteen the adenomatous hyperplastic type. There was one death. Following operation, increase in tolerance was rapid and in some cases, remarkable in degree. We have included two patients (Charts 1 and 2) in this group who possibly should be placed in the potential diabetic group. Their histories will be discussed later.

Blood sugar curves before and after operation were determined on a series of twenty selected patients who showed glycosuria in addition to hyperthyroidism. Sections of the thyroid showed eight with parenchymatous and nine with adenomatous hyperplasia, and three with cystic colloid goiters. The blood sugar curves of only five showed failure to go below 150 mgm. at the end of the second hour. There was apparently no relationship between the type of thyroid disturbance in the toxic goiters and the curve.

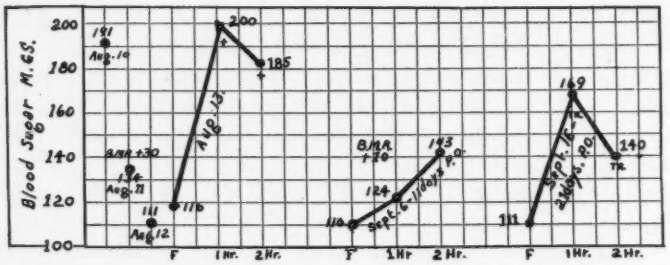
Using the diagnostic standards of Joslin and Lahey for the identification of diabetes associated with hyperthyroidism, we have included two

patients in our series of true diabetes, as stated above, who have shown, following thyroidectomy, return to approximately normal curves.

The first patient, case C. A. D. (Chart 1), age 56, housewife, came complaining of tachycardia, dyspnoea on exertion for two weeks, tremor of the hands for three months and weakness, sweating and loss of about ten pounds in a month. She stated that she had been eating considerable candy for three

CHART I

CASE—C. A. D. PATHOLOGICAL DIAGNOSIS—PARENCHYMATOUS AND ADENOMATOUS HYPERPLASIA

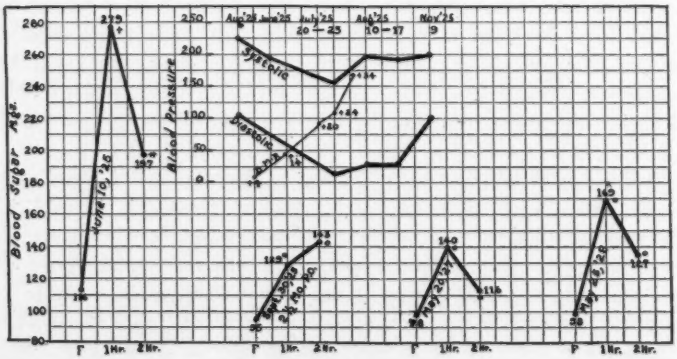


weeks. Sugar was found on routine urinalysis and the following morning her fasting blood sugar was 191 mgm. Reference to the chart will disclose the rapid return to a normal fasting level on a quantitative diabetic diet. The blood sugar curve the following day was certainly in the diabetic range. The basal rate at the same time was + 32 per cent. Following removal of the thyroid, and on an unrestricted diet the two curves taken perhaps a little too early can certainly not be called diabetic, nor are they entirely normal. Subsequent curves six months or a year later might have been entirely normal. That this has been our experience in other cases, the charts will show.

The second patient, case H. T. (Chart 2), housewife, age 53, was first seen in September, 1923, because of symptoms referable to hypertension and mod-

CHART II

CASE—MRS. H. T. PATHOLOGICAL DIAGNOSIS—PARENCHYMATOUS HYPERPLASIA



crate obesity. No sugar in the urine was discovered at that time and the fasting blood sugar was 90 mgm. Reference to Chart 2 will show the blood sugar curves on her second admission two years later when she presented symptoms of nervousness, weakness, thirst and polyuria of two months' standing. No

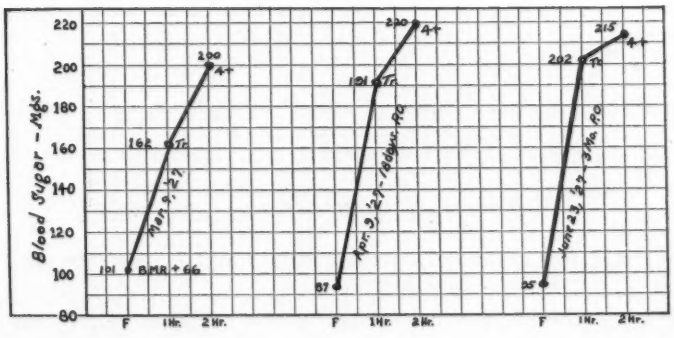
thyroid enlargement could be palpated and her symptoms were thought to be due to hypertension and a mild diabetes. A quantitative diabetic diet low in salt was started and the urine became sugar free immediately. Reference to the chart shows the falling diastolic blood pressure. Coincident with this a capillary pulse was first noticed and an increasing metabolic rate. Further search for a goiter was made and on stereoscopic chest films a substernal enlargement was seen which at operation proved to be a parenchymatous hyperplastic goiter. Two and a half months afterward on a diet unrestricted as to carbohydrate the blood sugar curve returned approximately to normal. Two years later it was entirely normal and a year later it was such as might be considered as representing a latent diabetes.

Wilder (4) mentions that there are a number of case reports in the literature which show return to normal tolerance following thyroidectomy. None of these, however, included blood sugar estimations after glucose meals. Gray (9) in 1923 reported a series of abnormal curves before and normal curves after removal of the thyroid. In Wilder's own case the patient had a fasting blood sugar of 271 mgm. and 60 gm. of sugar in the urine. One year following removal of 15 gm. of hyperplastic thyroid tissue, the curve was 110 mgm. fasting, 168 mgm. at one hour and 160 mgm. at two hours. He believes that on the basis of this evidence this patient had a latent diabetes.

Failure of the curve to return to normal following thyroidectomy is illustrated by case A. McL. (Chart 3). This patient, age 40, housewife,

CHART III

CASE—MRS. A. MCL. PATHOLOGICAL DIAGNOSIS—DIFFUSE PARENCHYMATOUS HYPERPLASIA

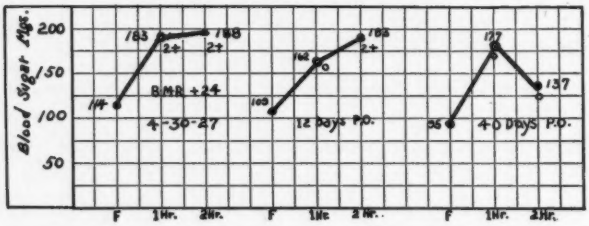


complained of nervousness, loss of weight and tachycardia for six months. No especial thirst or polyuria had been present. Both routine urines contained abundant sugar. Three months after removal of a parenchymatous hyperplastic goiter the curve showed even a higher second hour level than before operation. On the basis of experience in other cases one might have predicted a return to normal tolerance following operation. The results in this patient, however, demonstrate conclusively that one can not always predict the outcome.

A similar type of curve of lesser height is illustrated by case C. M. (Chart 4). This patient, a housewife, age 42, came with symptoms of

CHART IV

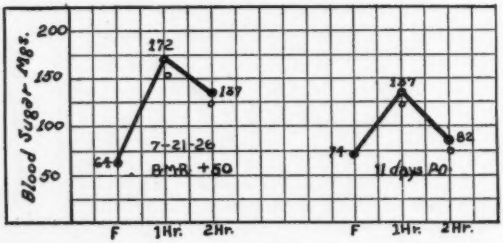
CASE—MRS. C. M. PATHOLOGICAL DIAGNOSIS—DIFFUSE ADENOMATOUS HYPERPLASIA WITH ADENOMATOSIS



nervousness and palpitation of ten months' duration without any of the classical symptoms of diabetes. Although the basal rate was only plus 24 per cent, the curve before operation is that of a potential diabetes. Forty days later it was in the borderline group quite similar to the final curve in case C. A. D. and the initial curve of case W. H. J. (Chart 5). The tendency for the second hour level to drop toward normal would seem to

CHART V

CASE—MRS. W. H. J. PATHOLOGICAL DIAGNOSIS—DIFFUSE PARENCHYMATOUS AND MODERATE ADENOMATOUS HYPERPLASIA



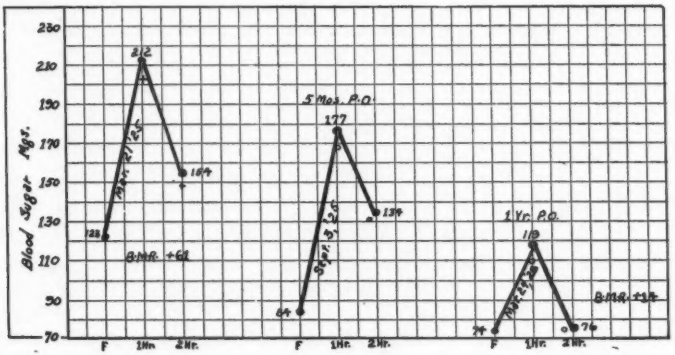
indicate that if a further curve had been taken six months or a year later it would have been entirely normal.

This contention is supported and illustrated quite clearly by the experience in case McC. (Chart 6) whose curve five months after operation is almost identical with that of case C. M. One year after operation it was entirely normal. This patient, age 40, a housewife, operated upon in 1921 for an adenomatous hyperplastic goiter, felt fine for a year; then her neck began to enlarge again and she lost weight. Her mother, age 60, has had diabetes for at least ten years. Here is our diabetic Anlage history clearly present in the mother, but the daughter with a hyperthyroidism in 1921 did not develop a diabetes, as the urines were sugar free at that time. The recurrent hyperthyroidism in 1925 had only a mild effect

on her tolerance despite the high metabolic rate of plus 61 per cent, and the final curve shows no evidence of a disturbed carbohydrate metabolism.

CHART VI

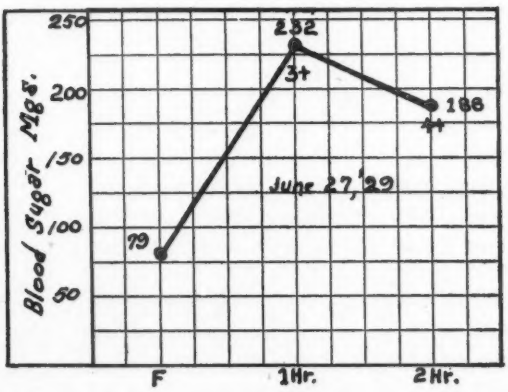
CASE—MRS. MCC. PATHOLOGICAL DIAGNOSIS—ADENOMATOUS HYPERPLASIA



A similar recurrent hyperthyroidism in case C. M. B. (Chart 7) is an illustration of disclosure of the diabetic Anlage in the father of a diabetic child who has been under our care for five years. This man, age 47, had a colloid adenoma removed in 1919, at which time no sugar was found in the urine. Again, in 1926, a double resection for a nodular adenomatous hyperplastic goiter was made. At this time the basal metabolism was

CHART VII

CASE—C. M. B. "COLLOID ADENOMA" REMOVED APR. 4, 1918. NODULAR ADENOMATOUS HYPERPLASTIC COLLOID GOITER REMOVED DEC. 3, 1926. B. M. R. + 24

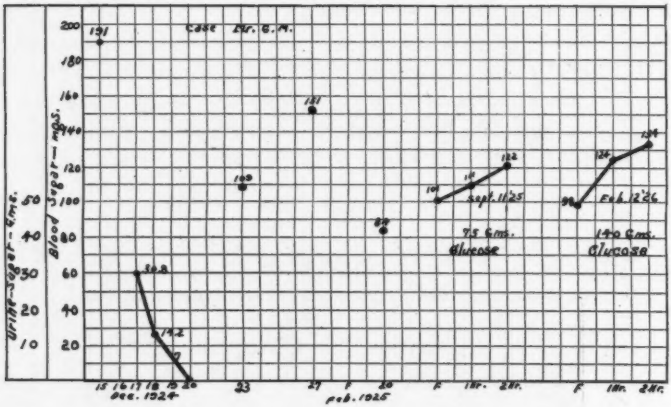


plus 24 per cent. Still no urinary sugar was present. In June, 1928, a trace of sugar was found, but none again until June, 1929, when a blood sugar curve gave the results shown on Chart 7. At that time no clinical

evidence of hyperthyroidism was present. The question arises as to whether this curve represents the residue of his old hyperthyroidism or evidence of a potential diabetes. Inasmuch as a hyperthyroidism ordinarily excites a latent diabetes and fans the flame, as it were, if this curve does represent a potential diabetes, why did not the two past instances of hyperthyroidism in his history precipitate it sufficiently to produce at least a glycosuria?

A third example of recurrent hyperthyroidism, not illustrated by a chart, bears a somewhat detailed report. A druggist, age 34, came in April, 1925, with symptoms of thirst and polyuria of a month's duration. A bilateral ligation for an exophthalmic goiter had been made elsewhere at age 22. He does not recall that anything was said about sugar in the urine at that time. Five years ago, at age 29, he was examined by a good internist who found sugar in the urine and obtained a blood sugar curve which the patient was told was normal and probably related to the goiter. Subsequent to this, in our records, the urine was negative for sugar. He had never been obese and there was no history of diabetes in the family. He

CHART VIII



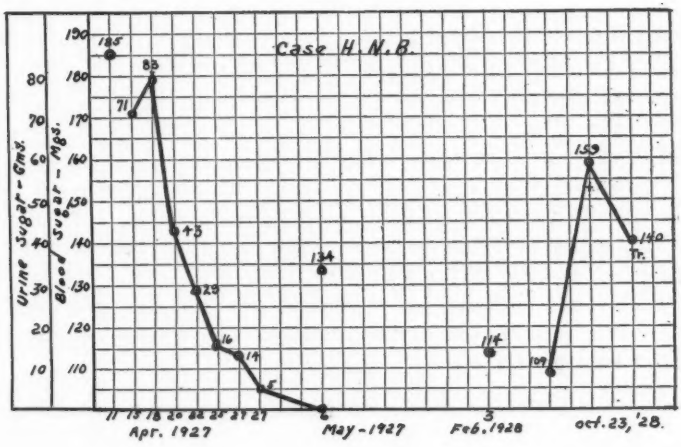
had, however, previous to the onset of the frank diabetes, eaten excessively of candy for four months, before this having been a heavy consumer of alcoholics. Examination revealed extreme emaciation, marked exophthalmos, tremor and sweating, and a toxic type of heart action. The basal rate was plus 36 per cent and the blood sugar 210 mgm. Seventy-five units of insulin daily was necessary to prepare him for operation. Subsequent to operation (pathological report: diffuse adenomatous and parenchymatous hyperplasia) his insulin dose was reduced to 40 units and his weight raised from 117 to 145 pounds.

If a diabetic Anlage is a prerequisite in every case of diabetes, why did not his hyperthyroidism at age 22 precipitate it? Was his glycosuria eight years later really a benign type? Is it possible that the most recent

hyperthyroidism at age 34 was really a more severe form and did the excessive carbohydrate intake, as suggested by John, produce irreversible changes in the islands of Langerhans?

The blood sugar curves of two patients with true diabetes, but without hyperthyroidism, are shown on Charts 8 and 9. The first patient, a laborer, age 44, without a history of diabetes in the family, had been tired for six months and had had thirst and polyuria for two months. He had lost in weight from 234 to 213 pounds in two months. He was still excessively overweight, being 5 feet 9½ inches tall. No doubt that a true diabetes

CHART IX



was present can arise from inspection of the chart, showing the initial blood sugar and the gradually decreasing glycosuria. Use of a quantitative diet for ten months and reduction of his weight to normal apparently had the effect of restoring a practically normal tolerance, at least as far as a blood sugar curve is concerned. Comparison of this curve with the second curve on Chart 1 reveals the fact that they are practically identical. Furthermore, undoubtedly were this patient with a restored tolerance subjected again to excessive food intake, obesity, infection, or a hyperthyroidism, a return of his diabetes would occur.

The second patient, Chart 9, a druggist, age 32, was also overweight approximately 30 pounds previous to the onset of his diabetes. The onset, moreover, dated from a period of financial worry. An uncle had diabetes. Classical symptoms ushered in the diabetes. Reference to the chart shows a blood sugar of 185 mgm. and, after a quantitative diet was started, a glycosuria of 81 gm. Without insulin he was desugarized in a month's time, and ten months later, maintaining his weight and a normal blood sugar on a diet of C-235, P-91 and F-98, he asked that a blood sugar curve

be plotted. Compare the result of this with the final curves on Charts 1 and 2 and mark the similarity.

Return of the tolerance to normal after institution of proper treatment in diabetes is, of course, not rare, as many cases of such have been reported in the past. Details of the above cited cases were given simply as a means of comparing the curves of diabetic patients without hyperthyroidism with those complicated with thyrotoxicosis.

We definitely know that a diabetic Anlage is present in both of these last mentioned patients. Have we any right to say from the evidence presented that a diabetic Anlage of mild degree does not also exist in the first two patients discussed?

The blood sugar estimations in this work were all made by the Shaffer Hartman method as modified by Haskins and Holbrook (10). The urine tests for sugar were made using the Benedict's qualitative reagent. The amount of glucose given the patients was 1.7 gm. per kgm. of body weight.

From the evidence obtained from the study of this small group of selected cases it should be evident that no conclusions may be drawn except that the diagnosis of diabetes in the presence of hyperthyroidism is not an easy or a settled problem. It is our opinion, however, that following thyroidectomy failure of the curve to return to normal after a sufficiently long time is indicative of the presence of a mild diabetes. For the time being at least, and until more is understood regarding this question, these patients will be treated as borderline diabetics and their blood sugar curves studied at least once a year.

SUMMARY

1. The literature regarding the problem of combined diabetes and hyperthyroidism is discussed.

2. A brief resume is given of the results in 24 thyroidectomized diabetic patients in connection with the pathological diagnosis.

3. The blood sugar curves before and after thyroidectomy in 7 patients with potential diabetes are presented with charts.

4. The blood sugar curves following dietetic treatment of two diabetic patients without hyperthyroidism are compared with the post-operative curves of the previous group.

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CO-EXISTENT DIABETES MELLITUS AND DIABETES INSIPIDUS WITH CASE REPORT

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On both theoretical and physiological grounds one would expect to find but few cases of diabetes mellitus and diabetes insipidus associated. A search of the literature reveals reports of but three cases. Surely others have been observed or existed, but I have been unable to find reference to them.

Gibson, Magers and Dulaney (1) report a case in a man, aged 69, and refer to a case reported by Lanter and Hiller (2) in which the highest blood sugar was 128. Steel (3) reports a case in a boy, aged 14. There are certain disturbing features about all of the above cases. That of Gibson et al showed marked fluctuations of urine output and sugar tolerance. The case of Lanter and Hiller showed a maximum blood sugar of only 128 mgm. Steel's case followed an encephalitis and likewise showed rather marked variations in sugar tolerance (4). In other words, there seems to be no continuity and uniformity of the progress of these cases, which fact raises the question as to whether or not they represent true or transitory metabolic imbalances.

From the literature, one gets a confused idea of the etiology of diabetes insipidus. Some writers think of it as a hyper-pituitarism, while others think of it as a hypopituitarism. At the same time one finds references that speak in terms of a dyspituitarism. Finally, some observers go beyond the pituitary and etiologically implicate the sympathetic nervous system. As with so many other conditions, the conclusion of the inquirer is that the entire truth is not yet known.

I wish to add to this chaos, a report of what appears to be a true case of diabetes mellitus associated with diabetes insipidus.

CASE REPORT

Mr. C. R. W., aged 40, white male, was born in the United States. His complaints when first seen by me were vomiting, diarrhea and blurred vision. These symptoms had been present off and on for three weeks, during which time he had lost between 25 and 30 pounds in weight. He weighed 98 pounds on admission to Baylor Hospital and was 69¾ inches in height. His blood sugar on admission was 333 mgm. per 100 cc. of blood. His urinary sugar was not quantitated but there was a large amount. His urine was likewise heavily positive with diacetic acid and acetone. His blood pressure was 94/64; temperature, 97° F., and pulse, 84. His blood picture showed 9,800 white cells with 71 per cent polymorphonuclears, 21 per cent small lymphocytes, 7 per cent large lymphocytes, and 1 per cent each of large monoculear leucocytes and transitional cells. His blood Wasserman and Kahn reactions were negative. His blood urea nitrogen was 10 mgm. per 100 cc. His phenolsulphonephthalein excretion was 58 per cent in two hours. The spinal fluid was normal in every respect.

Family History: A maternal grandmother had a severe case of diabetes, but died of la grippe. A maternal aunt died of diabetes mellitus at ten years of age. His father had a "nervousness or palsy" manifested as a twitching of the hands and feet. All of his father's brothers had the same condition. The patient has been bothered all of his life with the same trouble, though to a relatively mild degree.

Past History: As a child he had measles, mumps and scarlet fever, but no other notable illnesses. The first symptom noted relative to present illness was increased output of urine in December, 1922. The onset was very insidious. After about four months, however, he had reached a state in which he could not retain his urine longer than two hours. At this time, he was drinking inordinate quantities of water. The urine was examined but only for albumin. He lost ten pounds in weight and had a voracious appetite. Not until three months later was sugar found in the urine. He was advised to limit his diet. He became very nervous at this time, and remained about ten pounds under weight. He had several teeth removed, quit work and followed rigidly the diet outlined in his diabetic manual and remained sugar free. Although the total output of urine decreased during this time, the patient continued to void considerably more urine than normally. A few months later he became careless with diet and symptoms of weakness, cramps in the legs, disturbance in vision and easy fatigue with loss of weight developed. At this time, about two years after the onset of symptoms, he developed a cold. He noted at the time an output of from eight to nine gallons of urine in twenty-four hours. Insulin was started and given up to 20 units daily. Even with insulin and rigid dieting, he continued to void about 12,000 cc. of sugar-free urine each twenty-four hours. He remained sugar free for eight months. A few months later he had the remainder of his teeth removed. He changed his residence at this time and discontinued the insulin. Sugar reappeared in his urine. About three and a half years later, he noted he was voiding 12,000 to 16,000 cc. of urine daily with traces of sugar. He returned home (Texas) and recommenced insulin. He became sugar free but continued to void around 12,000 cc. of urine daily.

His progress from this point on varied about as described above until in February of this year when he developed a "spell of rheumatism." At this time he was drinking from six to seven gallons of water daily. He began to vomit and could retain nothing, he lost weight rapidly. He was first seen by me about three weeks after this upset.

Physical Examination: The patient appeared emaciated. Except for a slight edema of the feet and ankles, a careful physical examination revealed nothing of importance. He was promptly started on insulin and routine measures for the treatment of acidosis and quickly stopped vomiting.

COURSE

Diabetes insipidus was not suspected at all in the beginning. As soon as the patient's sugar metabolism was balanced, it was thought that his condition would immediately clear up. To my surprise, his urinary output steadily rose from about five liters to eighteen, with a perfectly negative urine. The specific gravity ranged from 1.002 to 1.003. Studies of his renal function were made and all constituents were found to be within normal limits. It was at this point that diabetes insipidus, associated with diabetes mellitus, was suspected.

Numerous tests were then instituted in order to study his response to the pituitary preparations. "Pitressin" was first used. The result was to the patient phenomenal. For the first time in several years he experienced sensations heretofore forgotten. His thirst disappeared, he had no tendency to void, his mouth became moist and his "bowels were enlivened."

Blood sugar and chloride determinations were made at intervals of 20 minutes following the first injection of pitressin. There was no significant variation of either metabolite throughout a three-hour observation.

"Pitocin" was next used. Blood sugar estimations were made at thirty-minute intervals following the injection. This pituitary extract likewise showed a very slight effect upon the blood sugar level; in fact, less than the pitressin. The subjective effect was not unlike that experienced when pitressin was given. The effect upon the patient's thirst and urinary output, however, was decidedly less than that produced by the pitressin. Next insulin and pitressin were given together. The blood sugar variations differed in no wise from those just described (see table for data).

Finally, "obstetrical pituitrin" was given. Whether the subjective sensation was a residual effect of the previously administered split substance or whether it was specifically a result of the pituitrin, the patient felt that this injection caused him to feel more normal than any of the previous injections. Consequently, he continued to use obstetrical pituitrin therapeutically with most satisfactory results, subjectively and objectively.

Strangely enough, a few days after the pituitary products had been started, the patient began having slight insulin reactions, although his diet and insulin had been unchanged for about ten days. His insulin was then reduced.

The reaction to the pituitary extracts were so sharp that it was thought that possibly some of the immediate effects at least might be a result of a circulatory congestion of the kidney. To test this possible effect, ephedrine sulphate in 3/8 grain doses was given every three hours. It has been shown that this substance actually causes renal congestion (5). During the twenty-four hours that the patient received ephedrine, his urinary output steadily rose and his familiar abnormal thirst returned.

It is notable that especially pitressin caused a marked retention of fluids. The patient, during the beginning of his observations, would frequently show a gain of as much as six pounds in one day. To illustrate this effect, he was allowed to recover from the effects of the pituitrin. A water test was then performed. In 4 hours following the ingestion of 1500 cc. of water, he voided 2,445 cc. About 12 hours later, he was again given 1500 cc. of water and immediately given 10 cu. mm. of pitressin. At the end of the 4 hours it was with difficulty that he voided 100 cc. of urine which had a specific gravity of 1.020. During this procedure, his feet and lower legs became markedly edematous.

Intradermal salt tests showed a rapid disappearance time, averaging about 25 minutes. The tests were made before the patient's water metabolism was balanced.

Before discharge from the hospital, the patient's sugar and water metabolism were balanced. He was discharged taking fourteen units of insulin before breakfast and eight units before supper. He was taking pituitrin (obstetrical) 10 cu. mm. t. i. d., midmorning, midafternoon and midnight. On this schedule, he was voiding from 1800 to 3000 cc. urine

daily and running a fasting morning sugar around 200 mgm. So many hypodermics being irksome, he was allowed to discontinue one pituitrin injection and advised to take this extract at noon and bedtime. Upon this regimen he has gained considerable strength and his weight has increased (in about four weeks) 30 pounds. After leaving the hospital, however, even with obstetrical pituitrin, three times daily, his urinary output increased. He has been advised to change to pitressin. He believes now that this substance has a more active and sustaining effect than the obstetrical pituitrin. He is at present taking two to three injections of ten cu. mm. of pitressin daily, midmorning and midafternoon and at bed time and is voiding from 2400 to 4000 cc. of urine each 24 hours. He has had to increase his insulin to 15 units twice a day. He is taking a diet of proteins, 70; fats, 175; carbohydrates, 125 gm. Detailed data are recorded in Table 1.

COMMENT

The etiology and pathological physiology of diabetes insipidus are not known, consequently there exists no unanimity of theory regarding it. One popular view is that diabetes insipidus is a result of deficient functioning of the posterior lobe of the pituitary body. Another is that it is a disturbance in the vasomotor tracts somewhere in the region of the hypothalmus. A third view combines these two hypotheses.

The glandular theory is inadequate, because it has been shown that diabetes insipidus can be produced in animals by traumatising the hypothalmic region without any demonstrable injury to the pituitary body (6). Equally difficult to reconcile, is the fact that in Simmond's disease, or pituitary cachexia, in which there is practically a complete atrophy of the pituitary body, there have not been recorded any symptoms to suggest diabetes insipidus. Indeed, the reverse is true (7).

Conflicting with the vasomotor view is the fact that pituitrin controls the symptoms of the disease. The effect of pituitrin seems largely metabolic and not mechanical.

The last theory correlates both the experimental and clinical data best. Sajous (8) describes two nerve paths which begin in the posterior or neural lobe of the pituitary and pass up via the infundibulum to the tuber cinereum. From here they course down the bulb, spinal cord and splanchnics to the kidneys and adrenals. He claimed that these pituitarorenal and adrenal nerves controlled renal circulation. Lepine (8) holds that lesions anywhere in this double tract that blocks the impulses through it to the kidney and adrenals cause passive dilatation of the renal vessels and polyuria or diabetes insipidus. Cushing (9) believes that the pituitary is involved through the influence affecting the nervous tracts passing from the spinal cord to the superior cervical sympathetic ganglion and posterior ganglionic fibres to the pituitary. In Rowntree's opinion, the whole truth

is not known as yet. He feels, however, that the pituitary gland exercises some control over kidney function.

TABLE I

DATA SHOWING DAILY PROGRESS OF PATIENT

First Admission to Hospital

1929 Date Feb.	Urine Vol. cc.	Sp. Gr.	Sugar	Diet P.	Diet F.	Diet C.	Weight Lbs.	Bl. Sugar Mgm.	Insulin U.	Remarks
16	.....	1.009	pos.	..	...	...	98	333	15	Patient vomiting.
17	3090	1.005	trace	24	55	58	98	83	10	Vomiting ceased.
18	5500	1.004	neg.	44	76	71	...	118 A.M. 154 P.M.	18	Condition improved.
19	4150	1.004	"	43	110	57	...	100 A.M. 100 P.M.	10	
20	6040	1.002	"	46	121	61	110½	160 A.M.	...	
21	6970	1.003	"	54	147	76	111½	173 A.M.	20	
22	7930	1.003	"	52	134	75	112	200 A.M.	27	
23	15300	1.004	"	50	127	76	114	148 A.M.	27	
24	12450	1.002	"	60	157	86	115½	...	27	
25	14940	1.003	"	65	170	85	121	111 A.M.	15	
26	13085	1.002	"	65	178	85	120	129	27	
27	15690	1.002	"	65	179	85	126	...	27	
28	18320	1.003	"	65	181	85	127	...	27	
Mar. 1	8710	1.004	"	65	181	87	127½	167	27	Pitressin, 10 m. at 2 P.M.*
2	10200	1.001	"	65	181	87	126½	...	37	Pitressin, 10 m. with 10 units of insulin at 2 P.M.†
3	7300	1.005	"	65	181	85	124½	...	27	Pitressin, 1 cc. at 2 P.M.
4	11418	1.005	"	64	171	77	125½	...	27	Pitocin, 12 m. at 2 P.M.‡
5	11280	1.005	"	65	181	85	124	...	22	Insulin reaction in A.M. and P.M. Pituitrin (0), 12 m., at 2 P.M.§
6	6840	1.007	"	65	181	85	118½	133	10	Pituitrin (0), 10 m., at 2 P.M.
7	17110	1.007	0.5%	65	181	85	114	182	10	Fedrin tried.
8	6000	1.009	0.6%	65	181	85	114½	286	15	Pituitrin (0), 10 m., t. i. d.
9	5450	1.008	0.5%	70	175	100	109½	200	15	Pituitrin (0), 10 m., t. i. d.
10	1760	1.008	trace	70	175	100	109½	...	15	Pituitrin (0), 10 m., t. i. d.
11	3000	1.009	"	..	...	...	110	235	23	Pituitrin (0), 10 m., t. i. d.
12	.....	.....	.....	..	...	...	111½	200	23	Discharged.

Second Admission to Hospital

1929 Date Mar.	Urine Vol. cc.	Sp. Gr.	Sugar	Diet P.	Diet F.	Diet C.	Weight Lbs.	Bl. Sugar Mgm.	Insulin U.	Remarks
25	1220	1.006	0.6%	70	175	125	...	211	27	Pituitrin (0), 10 cu. mm. t. i. d.
26	2780	1.015	1.2%	70	175	125	119¾	222	27	Pituitrin (0), 10 cu. mm. t. i. d.
27	3400	1.010	0.6%	70	175	125	120½	235	27	Pituitrin (0), 10 cu. mm. t. i. d.
28	7380	1.005	trace	70	175	125	...	222 A.M. 200 P.M.	27	Pituitrin discontinued.
29	7120	1.007	"	70	175	125	123½	...	27	Pituitrin (0), b. d.
30	7406	1.010	neg.	70	175	125	124	235	30	Pituitrin (0), 8 cu. mm. t. i. d.
31	3400	1.010	"	70	175	125	122½	...	30	Pituitrin (0), 8 cu. mm. t. i. d.
April 1	.....	.....	.....	..	...	...	120½	182	30	Discharged.

*Blood sugar reading before and each 20 minutes following the pitressin were: 118, 125, 118, 105, and 125. Blood chloride readings at the same intervals were: 459, 457, 475, 469, and 464. (Mgm. per 100 cc. of blood.)

†Blood sugar readings before and each 30 minutes following pitressin and insulin were: 105, 118, 133, 105.

‡Blood sugar readings before and each 30 minutes following pitocin were: 67, 105 and 118.

§Blood sugar readings before and each 30 minutes following obstetrical pituitrin were: 100, 133, 125 and 133.

Bourquin's (10) recent experimental work on diabetes insipidus is interesting, but does not help a great deal toward clearing away the obscurity surrounding the pathogenesis of this disease. Her work does certainly implicate the central nervous system, but in just what way remains to be determined.

One is impressed with the increasing importance of the relationship of the sympathetic nervous system with the endocrine system. It is difficult to separate the two systems functionally. When this functional relationship has been sufficiently examined, doubtless many apparent incongruities will be made clear and many gaps of knowledge filled.

Just why the patient reported in this paper should have diabetes mellitus associated with diabetes insipidus, I cannot say. The temptation to spin a theory of causal relationships is withstood, since, as Rowntree (11) has said, the field of internal secretion is already famous for few facts and many fancies.

From an endocrine viewpoint, I can see no reason for the co-existence of the two diseases. With an overactive pituitary gland one may expect and does find a secondary effect on other glands, notably the thyroid and pancreas (12). But in the case of diabetes insipidus, where the pituitary disturbance is not thoroughly understood—indeed may not even exist as a primary hypofunction or dysfunction, it is probably safer to consider the co-existence of diabetes insipidus and diabetes mellitus as purely a rare though fortuitous circumstance.

I wish to suggest and emphasize one point. Symptoms of diabetes insipidus, so generally considered to be a result of dehydration, are probably in large measure a result of pituitary-sympathetic nervous system disturbance. I refer to the dryness of the mouth, the dead feeling of the intestines, dry skin, etc.

In the case herein reported, the patient's own observation of the almost *immediate* disappearance of the "dead sensation" of the bowels, return of the moisture in his mouth, etc., following the administration of pituitrin, is, I think, significant. It is more probable that the constipation, dead sensation, as well as other symptoms, are a result of sympathetic nervous system disturbance with associated pituitary dysfunction; in other words, a primary instead of a secondary effect.

SUMMARY

A case of co-existent diabetes mellitus and diabetes insipidus in which different pituitary extracts were used is reported in detail. The observations suggest that pituitrin and insulin are not as physiologically antagonistic as ordinarily believed, at least in the presence of diabetes mellitus and diabetes insipidus.

Pitressin seemed to exert more of a blood sugar raising effect than did pitocin, and about the same as obstetrical pituitrin. Pitressin was the most active in controlling the symptoms of diabetes insipidus.

It is suggested that many of the symptoms of diabetes insipidus, such as constipation, dryness of the mouth, skin, etc., are a primary result of a sympathetic-pituitary disturbance and not a secondary result of dehydration.

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Reviewed in Endokrinologie, 2: 399. 1928.

The Glands of Destiny: A Study of the Personality. Ivo Geikie Cobb, 1928. Macmillan, N. Y. Pp. 302.

The book is roughly a mixture of "Why We Behave like Human Beings" and "Glands Regulating Personality." It is not so good as Dorsey and is better than Berman.

Traitement du goitre simple. Bargeat. 1927. Legrand, Paris.

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Reviewed in Schweiz. med. Wchnschr. 58: 811. 1928.

Abhangigkeit der Washstumsstorungen und Knochenerkrankungen von Storungen der inneren Sekretion. O. Maas. 1926. Carl Marholds. Halle a. S. Pp. 55.

Reviewed in Schweiz. med. Wchnschr. 58: 811. 1928.

Abstract Department

Contraction of the spleen and changes in the splenic blood produced by adrenin injection in animals (Contraction de la rate provoquée par l'injection d'adrénaline et comportement du sang splénique chez les animaux). Borysiewicz, A., Compt. rend. Soc. de biol. **99:** 931. 1928.

Blood from the splenic vein of dogs was examined. In 60% of cases, adrenin produced a splenic contraction which increased the red blood cell count markedly.—J. C. D.

Action of adrenin on calcium, potassium, and metabolic rate in normal cases and those with thyroid disorders (Action de l'adrénaline sur la dépense calorique, la calcémie et la potassémie chez l'homme normal ou atteint de troubles thyroidiens). Castex, M. R. and M. Schteingart, Compt. rend. Soc. de biol. **99:** 1649. 1928.

Injection of adrenin produced an equal rise in basal metabolism in both normal and sick individuals. No relation between this rise and variations in calcium and potassium could be observed.—J. C. D.

Adrenal syndrome in yellow fever (Syndrome surrénal dans la fièvre jaune). Chagas, E., Compt. rend. Soc. de biol. **99:** 1664. 1928.

The typical syndrome of adrenal insufficiency appeared in 10 to 15% of the cases on about the tenth day.—J. C. D.

The influence of desiccated suprarenal cortex and medulla on the growth and maturity of young rats. Chidester, F. E., A. G. Eaton and G. P. Thompson, Am. J. Physiol. **88:** 193. 1929.

Growth of young rats is retarded by 0.5 gram of either desiccated suprarenal medulla or cortex and is retarded, especially at first, by desiccated suprarenal cortex. Young female rats fed 0.5 gram of desiccated suprarenal cortex (as shown by earlier litters) reach sexual maturity sooner than controls or those fed on 0.5 gram desiccated suprarenal medulla daily. Males were not tested independently with older females so that it is not certain whether or not they reached sexual maturity earlier than the females of their own litter.—Authors' summary.

Effect of adrenal tissue on lecithin (Action du tissu surrénal sur la lécithine). daCruz, A., Compt. rend. Soc. de biol. **99:** 1530. 1928.

Fresh adrenal and liver tissue from guinea pigs was incubated at 37° in test tubes for 24 hours while in contact with lecithin. Both tissues split lecithin. The liver tissue is only slightly more active than the adrenal. Cholesterine added to the solutions intensifies the reaction.—J. C. D.

Oestrous cycle in adrenalectomized rats (Le cycle oestral du rat normal et décapsulé). Del Castillo, E. B., Compt. rend. Soc. de biol. **99:** 1403. 1929.

The operation did not interfere with the cycle nor with the age of opening of the vagina.—J. C. D.

The influence of suprarenal cortex and medulla on the growth and maturity of young (white leghorn) chicks. Eaton, A. G., W. M. Insko, G. P. Thompson and F. E. Chidester, Am. J. Physiol. **88:** 190. 1929.

The influence of adrenal cortex and medulla on the growth and maturity of young white leghorn chicks is discussed. Chicks fed desiccated suprarenal medulla grew almost the same as the controls for the first three weeks. After

that time their growth was less rapid than the controls. Chicks fed desiccated suprarenal cortex grew much more slowly at first than the controls. But by the end of the first eight weeks they began to grow more rapidly, and toward the end of the experiment almost equaled the controls in weight. If the weights of the testes are any indication of maturity, males receiving desiccated suprarenal cortex were more mature than either of the other lots, and those receiving desiccated medulla were less mature than those of the other lots. The average weight of the testes of the lot receiving desiccated suprarenal cortex was 0.2171 gram; the average of those receiving medulla was 0.1242 gram; while that of the controls was 0.2000 gram.—Authors' summary.

The diagnosis of adrenal tumors. Gibson, T. E., California & Western Med. **26**: 201. 1927.

A consideration of adrenal involvement is often forgotten in the diagnosis of abdominal conditions. Adrenal tumors give rise to three distinct clinical syndromes: (1) the genito-suprarenal syndrome, due to cortical tumors (carcinoma); (2) Hutchison syndrome, and (3) Pepper syndrome, both due to medullary tumors (neurocytoma). A knowledge of these renders the diagnosis of adrenal tumors comparatively easy, not only in differentiating them from other tumors, but also in distinguishing between the cortical and medullary neoplasms of the adrenals themselves. Unfortunately, most text books do not clearly portray these syndromes and the literature is fragmentary. Cortical carcinoma arises probably on the basis of cortical hyperplasia or adenoma formation. These benign precursors of carcinoma give rise to the same clinical picture of cortical adrenal tumor as does carcinoma itself. Neurocytoma is the common tumor of the medulla. It is often called "sarcoma" in the literature. Probably the vast majority of the retroperitoneal sarcomas of infancy arise in the adrenal medulla.—I. B.

Interrenin, the hormone of the suprarenal cortex (Interrenin, das Hormon der Nebennierenrinde [Vorläufige Mitteilung]). Goldzieher, M., Klin. Wchnschr. **7**: 1124. 1928.

The author believes he has isolated a hormone from the suprarenal cortex, which he calls "interrenin." The method of isolation is similar to that employed for insulin by Allen, Piper, Kimball and Murlin. The active principle is a white amorphous powder soluble in alcohol and in dilute acids and insoluble in distilled water, weak alkalies, ether and chloroform. The physiological properties are briefly as follows: Intravenous injection produces a fall in blood pressure acting as an antagonist to adrenalin. Injection of proportional doses of adrenalin and interrenin produces no effect on either the blood pressure or pulse rate. Interrenin produces a decrease in the blood lipoids, at times as much as 50 per cent diminution being obtainable in cholesterol and lipoid phosphorus. The maximum point is generally reached in an hour but at times the effect lasts longer, reaching the peak in two hours and beginning to decline after four hours. The material injected into rats which had undergone double adrenalectomy produced a prolongation of life for several months. Control animals without interrenin died within 14 days after a double adrenalectomy.—M. B. G.

The cephalic metastases of suprarenal blastomata in children. Grieg, D. M., Edinburgh M. J. **36**: 25. 1929.

The case was that of an eleven-months-old boy in which extensive exotoses occurred on the frontal and other bones near the orbit. These changes are shown in photographs.—J. C. D.

Variations in blood pressure in the head. Separation of the neuro-vascular from adrenal secretory reflex (Les variations de la pression artérielle dans la circulation céphalique. Déclenchement des réflexes neuro-vasculaires et adrénalino-sécrétoires). Heymans, C., Compt. rend. Soc. de biol. **99**: 1239. 1929.

Using the method of vascular anastamosis between dogs, the authors find that compensatory changes in blood pressure in the trunk rise from the stimu-

lus of low or high blood pressure acting on the carotid sinus and so through the sympathetic, on vascular tonus directly and also indirectly by producing a discharge from the adrenals.—J. C. D.

Adenoma of the adrenal cortex. Hicks, J. B., New England J. Med. **199:** 1140. 1928.

The tumor occurred in a woman forty-eight years old and was successfully removed. The patient showed diffuse yellow pigmentation, an unusual sign in this condition.—J. C. D.

Studies on the hyperglycemia following morphine injections: Rôle of the adrenals (Etudes sur l'hyperglycémie consécutive a l'injection de morphine. Rôle des surrénales). Houssay, B. A., J. T. Lewis and E. A. Molinelli, Compt. rend. Soc. de biol. **99:** 1408. 1929.

From extensive studies on dogs, the authors conclude that the adrenals respond to morphine by an increased discharge of adrenin. The adrenals play an active but not essential part in morphine hyperglycemia. When the medulla is removed instead of the entire gland, morphine hyperglycemia is after a time as intense as though the glands were intact.—J. C. D.

Formation of adrenaline-like substance in heart (Sur la formation dans le coeur d'une substance semblable à l'adrénaline par suite de l'excitation du nerf sympathique). Lanz, A. B., Arch. néerl. de physiol. **13:** 423. 1928. Abst., Physiol. Absts. **13:** 637.

The substance formed in the frog's heart on sympathetic stimulation shows several of the reactions of adrenaline in addition to accelerating another heart (it is not given up to the perfused Ringer's solution without sympathetic stimulation). Thus on perfusion through the frog's hind limbs it produces vaso-dilatation in very weak concentration and vaso-constriction in higher concentration; the amount present in the perfusing fluid depends on the intensity of the sympathetic stimulation of the heart. A weak solution of glycine dilates the frog's aorta, but increases the constricting effect of the unknown substance, similarly to its activating influence on adrenaline. The unknown also inhibits the rhythmic contractions of the isolated frog's stomach. It is destroyed by boiling, and gives Russmann's adrenaline reaction with sulphanilic acid and mercuric chloride. It is therefore adrenaline itself.

Intracardiac injection of epinephrine in a case of later postoperative embolism and heart failure. Lutaud, P., Bull. et Mem. de la Soc. des Chir. de Paris, **20:** 874. 1928. Abst., J. A. M. A. **92:** 937.

Lutaud reports a case of embolism and heart failure in a woman, aged 28, 10 days after a successful laparotomy. Epinephrin was injected intracardially from 8 to 10 minutes after the heart had stopped functioning, and in one minute after the injection one could observe the oscillations of the needle left in the heart region. After 10 minutes of artificial respiration the heart sounds became regular, and the patient started to breathe. She recovered without any further complications.

Suprarenal tumor with metastasis and optic neuritis. Mandel, L., Proc. Roy. Soc. Med. **22:** 646. 1929. (Sec. Dis. Child.)

This is a report of a case of sarcoma of the left suprarenal body with metastases to the skull and elsewhere, occurring in a girl of six.—I. B.

Changes in the arterial vaso vasorum in the rabbit following intravenous injections of adrenin (Modifications apportées par l'injection intraveineuse d'adrénaline a la circulation nourricière des parois artérielles du Lapin). The early microscopic changes in adrenin arterio-sclerosis (Les premières étapes histologiques de l'athérome adrénalinique expérimental). Ravault, P. P. and C. Bouysset, Compt. rend. Soc. de biol. **99:** 828. 1928.

A study of the absorption of trypan blue injected intravenously shows that the intima and inner zone of the media in the arteries are nourished

from the blood in the lumen of the vessel, while the rest of the wall is supplied by the vasa vasorum. The same method shows that following injection of adrenin, the vasa vasorum is constricted and, therefore, the blood supply of the external half of the media and that of the adventitia is interfered with. The initial permanent change in the walls of the vessels, as seen microscopically, is an oedema of the middle portion of the tunica media followed by deposition of calcium.—J. C. D.

On the effect of insulin administration upon the epinephrine content of the suprarenal body on rabbits. Saito, S., Tohoku J. Exper. Med. **12**: 263. 1929.

When insulin was administered to rabbits in a dose sufficient to cause convulsions, the epinephrine content of the suprarenal gland, determined by the colorimetric method of Suto and Inouye (14 cases) and of Folin, Cannon and Denis, and the rabbit intestine segment method (15 cases) showed a diminution, except in case of glands protected by denervation. When the same dose of insulin was given, with glucose simultaneously in adequate amounts, the diminuation did not take place in the epinephrine load in the suprarenal capsule with intact innervation.—R. G. H.

Significance of the augmented epinephrine secretion after haemorrhage in dogs upon the simultaneous occurrence of hyperglycaemia. Tachi, H. and S. Saito, Tohoku J. Exper. Med. **11**: 218. 1928.

Adrenalin was administered intravenously to splanchnotomized, unanaesthetized dogs at a constant rate corresponding to the rate of adrenin secretion following hemorrhage (as determined previously by the authors in experiments in which suprarenal vein blood collected from unanaesthetized dogs following partial exsanguination was assayed for its adrenin content). Infusion of adrenalin was quite regularly accompanied by the development of a marked hyperglycemia. The authors conclude that the increased adrenin output after haemorrhage is an important factor in producing the hyperglycemia which develops simultaneously.—R. M. Moore.

Lesions of the adrenal in yellow fever (Lésions des surrénales dans la fièvre jaune). Torres, C. M. and A. P. deAzevedo, Compt. rend. Soc. de biol. **99**: 1673. 1928.

The usual damage as seen in infectious fevers appears. The intracellular, doubly refractile, acidophile granules are unusually abundant.—J. C. D.

The action of adrenin and cholin on the blood pressure in decapsulated dogs (Action hémodynamique de l'adrénaline et de la choline chez les chiens surrénaloprives). Troilo, E., Compt. rend. Soc. de biol. **99**: 1521. 1928.

The sympathetic system is more sensitive to adrenin and the vagal system less sensitive to choline after adrenalectomy.—J. C. D.

Vagal function in adrenal insufficiency. Lack of vagal tonus (La fonction vagale dans l'insuffisance surrénale. Inexistence du tonus vagal). Viale, G., Compt. rend. Soc. de biol. **99**: 1522. 1928.

In dogs, decapsulization produces what may be considered a sympathetic hypertonus and a vagal hypotonus.—J. C. D.

Discharge of choline into the blood after injection of adrenin (Décharge de choline dans le sang après injection d'adrénaline). Viale, G. and T. Combes, Compt. rend. Soc. de biol. **99**: 1524. 1928.

The choline in the blood of the adrenal vein of dogs rises about 50% five or ten minutes after injection of adrenin.

Pneumin. A respiratory autocoid from the adrenal cortex discharged into the circulation via the lymphatics. Vincent, S. and J. H. Thompson, J. Physiol. **67**: 3. 1929.

Respiratory failure in decerebrate cats followed extirpation of both adrenals, ligation of the blood supply thereto, damage to the lymphatics behind the glands, or interruption of the thoracic ducts. Intravenous injection of fresh adrenal extract restored respiration while adrenalin did not. Destruction of all tissue connections with the adrenals except the lymphatics and the arterial supply did not affect respiration. Cautery of the medulla was without effect. The authors conclude that an incretion that is essential to normal respiration passes via the lymphatics. The name **pneumin** is suggested.
—C. I. R.

Virilism (masculinity) in a case of adenoma of the suprarenal cortex. Winkel, M., Deutsche Arch. f. Klin. Med. **159**: 1. 1928.

A report (with photographs) on a woman, aged 36 years, who had, over a period of 11 years, gradually developed the clinical syndrome of virilismus suprarenalis, namely, amenorrhea since the age of 26, obesity, heterosexual hypertrichosis, marked atrophy of uterus and ovaries, and hypertrophy of the clitoris. Such cases are rare but are recognized as due to hyperplasia (usually tumerous) of the suprarenal cortex. In addition Winkel's subject presented symptoms suggestive of hyperactivity of the suprarenal medulla, namely, hypertension (215-225 mm. Hg., systolic) with "blue red" cheeks, renal diabetes (glycosuria unrelated to dietary intake, and refractory to insulin), polyglobulism, and relative polymorphonuclear leucocytosis. The refractory reaction to insulin was interpreted as due to an excessive production of adrenalin. Suggestive findings by palpation and roentgenograms justified a diagnosis of right-sided adrenal tumor, which was corroborated at operation and proved to be an adenoma of the suprarenal cortex. It was readily removed but the patient died two days later. Autopsy revealed atrophy of both adrenals, ovaries and thyroid. The pancreas and hypophysis were normal.—H. L.

Carotid body tumor. Sellors, T. H., Proc. Roy. Soc. Med. **22**: 705. 1929. (Sec. of Surgery.)

This is a description of a case in a man aged 54 years. Swelling was first noticed in the neck following a dental abscess. A definite mass of enlarged glands at the angle of the jaw was noticed, and as the tonsils were manifestly septic they were removed. Hodgkin's disease was suspected but no further evidence of it could be found. The mass increased slowly in size and the patient lost weight. Tumor of the carotid body was confirmed by operation.—I. B.

A hormone mechanism for gall-bladder contraction and evacuation. Ivy, A. C. and E. Oldberg, Am. J. Physiol. **86**: 599. 1928.

An extract of the upper intestinal mucosa has been shown on intravenous injection to cause contraction and evacuation of the gall-bladder. The extract is free of vaso-dilatin and has no objective toxic effect on unanesthetized dogs. Cross-circulation experiments show that when acid is injected into the duodenum, something gets into the blood which causes the gall-bladder to contract. It is thought that this observation proves a hormone mechanism for gall-bladder contraction and evacuation. It is pointed out that other mechanisms may be concerned in gall-bladder evacuation. The terms "cholecystokinin" has been proposed as a name for the hormone and the active substance in intestinal extracts, which causes the gall-bladder to contract and evacuate. The amount of pressure that results from the contraction of the gall-bladder under the influence of "cholecystokinin" is for one injection a maximum of 11.5 cm. of bile pressure and a minimum of 1.0 cm., and for a series of injections an average of 10.0 cm. and a maximum of 22.5 cm. in anesthetized dogs; and in unanesthetized dogs for a series of injections it is an average of 20.0 cm. of bile and a maximum of 24.0 cm. of bile. The average duration of the contraction for a single dose is 15 minutes. Following a series of doses the gall-bladder relaxes in from 30 to 60 minutes. The injection of the following

substances into the duodenum of the dog caused the gall-bladder to contract with the animal under light barbital-ether anesthesia: 15 to 40 cc. of N/10 HCl, 30 cc. of butter, digested egg-yolk, cream of olive oil, 0.5% butyric acid, and 5% soap solution. Undigested olive oil, egg-yolk and cream were ineffectual. Spontaneous rhythmic contractions of the gall-bladder were observed to occur from 2 to 4 times a minute. A small dose of "cholecystokinin" would usually increase their amplitude to as much as 3 cm. of bile pressure; a large dose would usually cause them to disappear at the height of the contraction, but they would reappear some time during the period of relaxation. If they were not present prior to the injection, they would frequently appear during the latter part of the period of relaxation. It has been observed that the hepatic ducts are injected with lipiodol during the contraction of the gall-bladder, the injection of the ducts being due, it is thought, to increased (abnormal?) tone of the duodenum or sphincter of Oddi.—Authors' Abst.

Endocrine disturbances in infant and adolescent psychopathics. Their relation to hereditary syphilis (Les troubles endocriniens dans les psychopathies de l'enfance et de l'adolescence. Leurs rapports avec l'heredo syphilis). Drouet and Hamel, Rev. franç. d'endocrinol. **7**: 1. 1929.

Examination of some 108 known psychopathics showed certain syphilitic ancestry for 92 or about 90%. Improvements in some cases were produced with thyroid and acetylarsan.—B. C.

Tinnitus aurium; its incidence in endocrine disorders. Drury, D. W., J. A. M. A. **91**: 1508. 1928. Abst., J. A. M. A.

Analysis made of 1,000 cases at the Evans Memorial, 585 of which were demonstrably endocrine, showed an incidence of tinnitus in 35.6% of the endocrine cases and 32.7% in the non-endocrine cases. Further analysis of the non-endocrine group showed an appreciable percentage of diseases in which tinnitus is a characteristic or frequent symptom. It is concluded that while tinnitus aurium is not a characteristic symptom of ductless glandular affections, it is encountered equally often in hypofunction of the endocrine glands.

An investigation of the effect of glandular therapy on the intelligence quotient. Fox, Edna J., Ment. Hyg. **12**: 90. 1929.

The article attempts to present some definite material on the relation of glandular therapy to intelligence in terms of I. Q. One hundred and eighty-two patients were diagnosed as suffering from some definite endocrine dysfunction involving one or more glands and in each case some glandular therapy was prescribed. The majority of subjects ranged in age from 3 to 16 years. One hundred and one were diagnosed as hypothyroid, 3 as hyperthyroid, 23 hypopituitary, 2 hyperpituitary, 3 thyro-pituitary and the remaining 50 as pluriglandular. The intelligence quotient for each individual was established by means of the Terman Revision of the Binet-Simon Intelligence Test, the average I. Q. being 74, the lowest 30 and the highest 115. The hyperthyroid cases were the most intelligent, the hyperpituitary the least. In 22 cases a second and third psychological rating was secured after from 4 months to 2 years of glandular treatment. Ten of these rated lower and 12 higher than on the first test, the greatest gain for any individual being 11 points. The pluriglandular group showed the greatest gain. While the subjects profited physically and emotionally from the glandular treatment, there was no perceptible variation in their intelligence quotients.—Gertrude Hoskins.

Detection and action of a circulatory hormone (Nachweis und Wirkung eines Kreislaufhormons). Frey, E. K. and H. Kraut, München. med. Wchnschr. **75**: 763. 1928.

The authors give a summary of their work up to the present time on what they term the circulatory hormone. It was first noted that the intravenous injection of human or animal urine regularly produced lowering of the blood pressure, an increase in the amplitude of the pulse and usually an increase in

the heart rate. These effects last from one-half minute to ten minutes. The substance has some similarity to histamine, but the authors believe it is a different compound. Histamine produces an increase of blood pressure in rabbits and an increase in the liver volume of dogs; two effects which are not obtained with their material. The hormone becomes inactive when mixed with blood. This inactivity, however, is due not to destruction, but to a combination with the blood. The combination can be again broken down by treatment with papain. The kidneys have the ability to activate the hormone when it is inactive.—Ralph H. Major.

The influence of endocrine secretions and of alkaloids on the permeability of animal membranes (Ueber den Einfluss von Inkreten und vegetative Giften auf die Permeabilität tierischer Membraner). Gellhorn, E. and Hilde Gellhorn, Arch. f. d. ges. Physiol. **221**: 247. 1928.

Permeability of muscle and skin membranes to sugar is increased by adrenine 1:1,000,000, by thyroxine (from 1:10,000 to 1:1,000,000), and also by insulin.—A. T. C.

Muscle chemistry under the influence of endocrine secretion and of poisons (Der Muskelchemismus unter dem Einfluss von Inkreten und Giften). Handovsky, H., Arch. f. d. ges. Physiol. **220**: 782. 1928.

Lactic acid and carbohydrate content of muscle depend, amongst other factors, on the adrenal secretions (especially in male animals) and the testes.
—A. T. C.

Endocrine factors in dementia praecox. Hoskins, R. G., New England J. Med. **200**: 368. 1929.

Fifty-three outstanding papers in the literature are reviewed. The survey leaves one with the overwhelming impression that scarcely a single detail has been satisfactorily established. Only a beginning has been made in determining the significance of the possible endocrine factors in dementia praecox. That the sex life and habitus are frequently abnormal is fairly definitely established. This correlates with the fact that the primary sex glands very commonly give histological evidence of degenerative changes or of aplastic development. The fact that similar changes are found in states other than dementia praecox signifies merely that in these conditions, too, gonad failure may play a rôle. A similar comment may be made on the degenerative conditions reported in the adrenals, the pituitary and the thyroid. The fact that such conditions are not found in all cases of schizophrenia would seem merely to indicate that endocrine deficiency is not the sole cause of the disease, though it may well be an important contributory factor. To determine the matter we must have many more exhaustive diagnostic studies. These must be rounded out by equally exacting therapeutic tests. The fact that more than one-sixth of all hospital beds in the United States are devoted to victims of dementia praecox constitutes this disorder the most insistent challenge to American medicine. In meeting this challenge much more work must be devoted to a determination of the part played by endocrine factors in its causation and of the possible value of endocrine substance in its treatment.
—Author's Abst.

The endocrinology of tuberculosis. Obermer, E., Proc. Roy. Soc. Med. **21**: 329. 1928.

The author suggests that the endocrines hold the key position in the mechanism of resistance to infection. In man the glands of internal secretion are divided into two counterbalancing groups. It is the function of the "katabolic" group—or glands of emergency—to react to acute infections. It is the function of the "anabolic" group—or glands of conservation of energy—to counterbalance the prolonged overaction of the katabolic group in chronic infections. In chronic pulmonary tuberculosis improvement is dependent on the predominance of the anabolic group. Clinical and biochemical evidence to this effect is offered. The individual ductless glands are discussed with a

view to summarizing the known tests for detecting their functional variations during life. The classification of cases of pulmonary tuberculosis according to the mode of endocrine reaction rather than to the extent of lung invasion is advocated. Emphasis is laid on the necessity for research into the heredity and environmental factors which lead to injury of the ductless glands, and hence lowered resistance to disease.—I. B.

Clinical study of mongolian idiocy (Zur klinik der Mongoloiden Idiotie). Orel, H., Ztschr. f. Kinderh. **44**: 448. 1927.

This study is based upon clinical observations of 95 patients, of whom 54 were males and 41 females. Only 14 were above 10 years of age. The author feels that the incidence of Mongolian idiocy in Vienna is not very great, as in a survey of two institutions housing 600 mentally defective children, only 5 were Mongolian idiots, an incidence of less than 1%. There has been an increase in the incidence of this condition in the past few years. It has been found in all European races and also in Negroes and in Chinese. The patient was the product of the mother's last pregnancy in 51 cases (86%) and of the only pregnancy in 11 instances (12%). In 59% of the cases, the age of the parents was between 35 and 49 years. A familial history of some mental delinquency was found in 14 families. The condition of the thyroid in the patients under study revealed no abnormal findings. The cardiac condition was generally normal. There was an incurving of the little finger in the majority of children. The delinquencies found were in mentality, walking and talking. There seemed to be a love of music. The author refers to the slit between the anterior and middle clinoid processes of the sella turcica described by Timme but feels that the investigations of Cliff and of Gordon and Bell have shown that this slit is not characteristic of Mongolian idiocy. The treatment consisted of thyroid, thymus and pituitary extracts resulting in some improvement in special symptoms but not in the general condition.—M. B. G.

Endocrine imbalance and its reaction to chronic arthritis. Pringle, G. L. K., Brit. M. J. **1**: 751. 1928.

The author has noticed the frequency of occurrence of rheumatoid arthritis in patients in whom an endocrine imbalance can be demonstrated. He quotes the experience of others who have likewise noticed this relationship. Especially is this true during pregnancy and the menopause. The association of arthritis with infections and septic foci is explained on the basis of an unstable thyroid-adrenal apparatus. The effect of infections on the thyroid gland is well known. In a similar manner vaccines and protein shock are at times beneficial because they stimulate the thyroid-adrenal apparatus, "sympathetic fever" being one of the normal reactions of the body against infections.

—N. A. Womack.

Treatment of obstinate obesity. Shepardson, H. D. and R. E. Allen, California & Western Med. **26**: 33. 1927.

In the cases discussed the basal metabolism, as determined by the ordinary methods, was within normal limits, yet it was apparent that the actual metabolism was decidedly abnormal. In each instance the diet was reduced to a level considerably below the basal requirements without impairment of health, and a definite loss of weight resulted, beyond which further reduction was unobtainable by dietary restriction alone. The subsequent addition of the indicated glandular medication resulted in further loss of weight and permitted an increase in the diet to a point where moderate exercise produced no untoward effect, i. e., exercises which might have been harmful with the previous extremely low caloric intake. Thyroid extract was used as a general stimulant to metabolism rather than to supplement a thyroid deficiency. After the return to normal weight or to a point slightly below the calculated normal, there may occur a rearrangement in the weight control mechanism which will result in a maintenance of normal stature without undue limitation in diet. This form of treatment is not advocated in all cases of obesity, but in the more difficult cases when patients could be kept under close observation.—I. B.

On the internal secretions of the salivary glands (Sulla secrezione interna delle ghiandole salivori). Simonetta, B., Arch. Scienze Med. **49**: 10. 1927.

After a careful and complete review of previous work in this field, the author describes his several experiments on rabbits deprived of parotids, submaxillary and infraorbital glands. The results, while not sufficient to deny endocrine activity of the glandular tissue as a whole, suffice to exclude with certainty that such an activity only belongs to parotids, submaxillary and infraorbital glands.—G. V.

Functional heterotransplantation of endocrine glands (Über d. Funktion endokrinen Heterotransplantation als Kennzeichen ihrer Einheilung). Voss, H. E., Biol. generalis, **3**: 571. 1927.

Hitherto the result of heterotransplantations of various organs has been determined by microscopical methods. Voss introduces a functional test to replace or supplement the histological test in the case of heterotransplantation of certain endocrine glands, such as ovary or placenta. He transplants into rats pieces of human placenta or ovaries of mice. The hormones, either preformed in these tissues or produced by them following transplantation, call forth changes in the vaginal smear which are characteristic of proliferative processes in the vaginal epithelium like those initiated by the follicular hormone. Within the first few days following transplantation the preformed hormone enters the host organism and here exerts its typical effects (in the immature, and in same cases also in the castrated, rat). This is followed by a period of rest. Voss observes that a second period of sexual activity takes place which begins about 10 days following heterotransplantation, reaches an optimum at 18-19 days and may still be noticeable as late as 36 or even 45 days. The latest term at which some living cells were observed was 19 days after transplantation, in the case of the placenta, and 29 days in the case of the ovary. In the later periods of placental transplantation the author states that the identification of the remaining cells was not certain; he believes, however, that he had to deal with Langhans' cells. In the case of the ovary only some atretic follicles and interstitial cells were left. He concludes that these cells begin to function in the strange host organism at this relatively late date, after they have become adapted to the new environment. He believes, therefore, that the functional is superior to the histological test, as an indicator of the living condition of the transplanted tissue.—Leo Loeb.

A new method for the stimulation of endocrine glands with radium. Wolf, W., Am. J. Roentgenol. **15**: 520. 1926.

Radium is distributed evenly over an area of 2 by 4 inches in a specially constructed applicator. Various types of filter may be interposed between the radium and the body to be irradiated. In every instance a hard rubber plate is interposed to absorb the secondary radiations. The length of time is 1 to 15 minutes for each gland. The distance is from 2 to 15 cm. Definite results were obtained in irradiation of the thyroid, ovaries, pituitary, testicles, and parathyroids. The results with the pineal and Islands of Langerhans were uncertain. Small doses, 0.01 to 0.1 of an erythema dose, increase the amount of glandular secretion poured into the blood stream, while large doses diminish the output.—M. B. G.

Concerning the active materials of the ovary (Ueber die Wirkstoffe des Ovars). Biedl, A., Arch. f. Gynäk. **132**: 167. 1927.

After a short critical review of the preceding work, Biedl reports the results obtained with the oestrous hormone in his own researches. He defines the unit of this hormone as that least amount which injected into castrated mice 3 times at 12 hour intervals produces the oestrous stages of the vaginal smear. He succeeded in obtaining the hormone in a water soluble form, highly purified from follicular liquid, follicle walls and the remaining ovarian tissues by a process which depends upon the capacity of the hormone of going to the cathode upon electrodialysis. The clinical test showed the possibility of improving certain forms of amenorrhoea with small amounts injected subcutaneously and of influencing favorably the climacteric discomforts by oral

use. The dosage varied from 2-4 mouse units. In the search for the inhibiting hormone of the corpus luteum Biedl was able to find a criterion of activity but has not succeeded in obtaining the hormone itself.—Winter. Translated by J. Gagnon.

Notes on a new hormonal test for pregnancy (A propos d'un nouveau test hormonal de la gestation). Brouha, L., H. Hinglais and H. Simonnet, Compt. rend. Soc. de biol. **99**: 1384. 1929.

Subcutaneous injections of human urine were given immature female mice of 6 to 8 grams weight. After 5 days they were killed and examined. Definite histological changes in the ovaries and genital tract always indicated that the urine was from a pregnant woman. Lack of such changes was absolute evidence of non-pregnancy. Certain animals showed an equivocal reaction which left the diagnosis doubtful. Anterior lobe secretion from the hypophysis may be the hormone responsible for these reactions.—J. C. D.

Action of liposoluble extracts of testis on the female genital tract (Action d'extraits orchitiques liposolubles sur le tractus génital femelle). Brouha, L. and H. Simonnet, Compt. rend. Soc. de biol. **99**: 41. 1928.

Liposoluble extract of bull's testis produces in rats precocious puberty with the accompanying changes in the ovary and in spayed animals a return of normal oestrous.—J. C. D.

Results of total ligation of the testicular pedicle in the domestic cock (Les effets de la ligature totale du pédicule testiculaire chez le coq domestique). Caridroit, F., Compt. rend Soc. de biol. **99**: 1311. 1929.

Such ligation produces only temporary castration. Circulation is re-established through the periphery and enough testicular tissue eventually survives to act as a testicular graft and maintain male characteristics.—J. C. D.

Can the testis produce female plumage in spayed domestic hens? (Le testicule peut-il féminiser le plumage d'une poule ordinaire ovariectomisée?). Caridroit, F., Compt. rend. Soc. de biol. **99**: 1632. 1928.

Spayed hens showed, after moulting, cock feathering and then after two years a change to hen feathering. Autopsy showed the right gonad to be a true ovo-testis. The ovarian tissue had apparently developed later than the testicular.—J. C. D.

Effect of splenectomy and pinealectomy on the oestrous cycle in white rats (Action de la splénectomie et de l'épiphysectomie sur le cycle oestral du rat blanc). del Castillo, E. B., Compt. rend, Soc. de biol. **99**: 1404. 1929.

Splenectomy did not affect the cycle and pinealectomy did not modify body growth or the age at which the vagina opened.—J. C. D.

Reappearance and character of the oestrous cycle following ovarian grafts in spayed white rats (Réapparition et caractéristiques du cycle oestral après greffe ovarienne chez le rat blanc castré). del Castillo, E. B., Compt. rend. Soc. de biol. **99**: 1501. 1928.

The initial cycles beginning a week after the graft were marked by a shortening of the dioestrous and a prolongation of the active periods. Later cycles were normal.—J. C. D.

Insulin and folliculine (Insuline et folliculine). Courrier, R., Compt. rend. Soc. de biol. **99**: 1630. 1928.

Insulin alone does not produce oestrous in spayed animals, nor does it in any way modify the action of folliculine when injected with it. Folliculine causes abortion in rabbits. Insulin does not interfere with pregnancy.—J. C. D.

The influence of vitamin A deficiency on the oestrous cycle of the rat. Coward, Katherine H., J. Physiol. **67**: 26. 1929.

A vitamin A-free diet was irradiated to generate vitamin D and fed to two groups of rats, (a) young whose stores of vitamin A were depleted from early life, and (b) mature rats whose stores were unknown but not large. None had had opportunity for mating. While many results on young rats confirm other investigations, variations from these results were so great that this test is considered questionable as a criterion of vitamin A deficiency. Mature rats, placed on the diet, showed normal cycles for some time, but finally vaginal smears showed only leucocytes and later only cornified cells. No ovarian abnormalities were found at autopsy.—C. I. R.

Experimental homeoplastic transplantation of testes. Demel, R., Arch. f. klin. Chir. **150**: 1. 1928.

The author deals with the question of persistence and growth of homoplastic testicular transplants. In ten rats he grafted entire testes within the tunica vaginalis. The site of these transplants was prepared by removal of the normal testis. These transplants did not persist but degenerated. In each of 16 rats he prepared a site in the scrotum for reception of a testis graft. This was done by scarification of the tunica propria, thereby provoking production of granulation tissue. When entire testes were transplanted into such areas they persisted and grew. He concludes that vascularization is the chief difficulty where persistence and growth are not obtained.—R. M. Oslund.

The female sex hormone. IX. Possible significance of the rodent vaginal spread reaction in the male blood. Frank, R. T., M. A. Goldberger and L. C. McGee, Am. J. Obst. & Gynec. **16**: 387. 1928.

In 60 blood samples from 47 male patients, 3 gave a threshold reaction by means of vaginal smear test in the spayed mouse, and 4 gave a doubtful (weak) reaction. All attempts to obtain a positive reaction with testicle extracts have proved negative, including testicle extracts which increased the growth of combs, wattles and ear lobes of capons. In spite of the positive reactions from male bloods, we consider the rodent vaginal smear reaction specific for the female sex hormone. No explanation is as yet offered for the occasional positive reaction in the blood of males.—R. T. Frank.

The effect of x-radiation on the spermatogenesis of the guinea-pig. Gatenby, J. B., Proc. Roy Soc. **104**: 351. 1929.

The effect of roentgen rays on cell mitosis is due to the destruction of lipoidal substances necessary for mitosis. The centrosome does not seem to be sensitive to the rays.—E. L.

Experimental overfeminizing and its effect on the sex of the offspring (Experimentelle Hyperfeminierun und ihr Einfluss auf das Geschlect der Nachkommenschaft). Gostimirovic, D., Biol Zentralbl. **49**: 24. 1929.

Working on white mice, with a series of 50 control and 92 treated females, this investigator found that subcutaneous injection of an ovarion hormone, (Follikulin-Menformon) was followed by an increase of approximately 20 per cent in the ratio of males to females of the offspring. It is suggested that enlargement of the uterus at oestrus resulting from administration of the hormone favored the presumably more motile male-determining sperms. The results also make it more probable that the female white mouse is homogametic while the male produces two kinds of sex-cells.—E. P. D.

Ovarian extract after artificial menopause. Haultain, W. F. T., Edinburgh M. J. **35**: 180. 1928.

In practice, ovarian extract by mouth reduces the unpleasant symptoms. If this is supplemented by injections of ovarian extract, the results are better. —J. C. D.

The oestrous hormone in the urine of pregnant cows. Hisaw, F. L. and R. K. Meyer, Proc. Soc. Exper. Biol. & Med. **26**: 586. 1929.

In the urine of pregnant cows the amount of the oestrous producing hormone increases as pregnancy progresses. In general in the later days of pregnancy great amounts of the hormone may be excreted. One cow on the 280th day of pregnancy excreted more than 6,000 rat units. Within the first 24 hours after parturition, little or no hormone was eliminated.—M. O. L.

Observations on menopause; effects of various ovarian preparations on symptoms of menopause and on basal metabolism. King, J. T. and Ellen Patterson, J. A. M. A. **91**: 1423. 1928. Abst., A. M. A.

The effects of various ovarian preparations on symptoms of the menopause and on basal metabolism were studied. The authors concluded that corpus luteum and whole ovary by mouth and follicular extract subcutaneously are probably useless in the relief of symptoms of the menopause. Bromide or phenobarbital or a combination of the two is distinctly helpful in the treatment of such symptoms, probably not specifically but as general mild sedatives. Corpus luteum may raise a low metabolic rate in a patient at the menopause, but this effect is not sufficiently striking or constant to warrant definite conclusions. Fresh whole gland and follicular extract seemed to have no significant effect on basal metabolism.

The action of the ovarian hormone on glycemia in normal dogs (L'action de l'hormone ovarienne sur la glycémie du chien normal). Rathery, F., R. Kourilsky and S. Gilbert, Compt. rend. Soc. de biol. **99**: 529. 1928.

In bitches, folliculine increases the glycemia produced by feeding fasting animals 20 grams of glucose. In males, the blood sugar is reduced.—J. C. D.

New experiments on experimental hermaphroditism and the antagonism of the sex glands (Neue Untersuchungen über experimentellen Hermaproditismus und über den Antagonismus der Geschlechtdrüsen). Lipschütz, A., Arch. f. d. ges. Physiol. **221**: 439. 1929.

Ovaries intrarenally implanted into 14 male guinea-pigs with intact testes gave in 3 cases an ovarian effect on the mammary apparatus; in 2 animals a secretion of colostrum and milk resulted.—A. T. C.

Experimental therapeutics of oestrous failure (Experimentelltherapeutische Studien an Weibchen mit spontaner Zyklusinsuffiziens). Loewe, S., H. E. Voss and E. Paas, Endokrinol. **1**: 323. 1928. Abst., Physiol. Absts. **13**: 664.

Transplantation of anterior pituitary into female mice in which cessation of the sexual cycle has spontaneously occurred almost invariably brings on an oestrous period. The effect is independent of the amount of gland substance transplanted. Tyramin, histamine, and a synthetic zykloäthanamin are unable to produce this result.

Pseudohermaphroditism (female type predominating). Manning, J. B., S. Robinson and N. H. Brush, Am. J. Dis. Child. **35**: 862. 1928.

The patient was an eleven-year-old child showing external genitalia of both sexes. Pubic hair appeared at ten years of age and enlargement of the mammary glands two months previous to the time of reporting. There was a moderate hypertrichosis on the upper lip, both arms and thigh. The pubic hair was triangular in distribution with an abundance of crotch hair. The phallus was 7 to 2 cm.; the body consisting of two corpora cavernosa; there was a tiny meatal non-patent opening at the tip of the glans with, however, a hypospadia. The vaginal opening was of normal appearance. A laparotomy performed to determine the true sex revealed a rudimentary uterus with apparently normal tubes and ovaries, one ovary showing a cystic formation. No masses were felt in the region of the kidney. The sex of the child was considered as female and the phallus was removed. Microscopic examination of the latter showed erectile tissue, but nothing distinctive as to sex in the corpora cavernosa.—M. B. G.

The effect on growth and metamorphosis of feeding ovarian tissue from normal (laying) and brooding hens to frog tadpoles (Der Einfluss der Zurfuhr von Ovarium der normalen Henne und der Bruthenne auf das Wachstum und die Metamorphose der Kualquappen dwes Frosches). Moschini, D. G., Endokrinologie, **3**: 29. 1929.

Eighty-six tadpoles were divided into 4 groups. Group 1 were fed beef heart and normal ovary; group 2, beef heart and ovarian substance from brooding hens; group 3, beef heart and normal hen flesh; group 4, beef heart and flesh from brooding hens. Both ovary and flesh from brooding hens produced earlier development than that from a normal or laying hen. The ovarian tissue in both cases caused earlier development than the flesh.—B. C.

The effect of the corpus luteum on the continuance of pregnancy (Rapporti fra funzione del corpo luteo ed evoluzione della gravidanza). Ottorino, Da Re, Arch. di fisiol. **26**: 243. 1928.

Rabbits, in which the stages of pregnancy were known, were used to determine whether the ablation of the corpora lutea affected the continuance of pregnancy. Three animals were ovariectomized at 10 days of pregnancy and 4 animals at 20 days of pregnancy. All 7 aborted their young in from 2 to 6 days after the operation. Six control animals, 3 of which were in 10 days of pregnancy and 3 in 20 days of pregnancy, were opened laterally, followed by manipulation of the uterus and ligation of the ovarian peduncle. There was no abortion in the control group. In other experiments the destruction of the corpora lutea by cautery in 8 animals which were in 10, 11, 20, 21 and 22 days of pregnancy aborted their young in all cases. Three control animals in 10, 11 and 22 days of pregnancy received similar treatment, except portions of the stroma of the ovary were cauterized instead of the corpora lutea. Two of the controls gave birth to living young and one aborted after having contracted peritonitis from the operation. The presence of only 2 corpora lutea at the tenth day of pregnancy was sufficient to prevent abortion, while in another animal the presence of parts of corpora lutea were not sufficient to prevent abortion. The cauterization of the corpora lutea of one ovary and not the other seemed to cause abortion. The ovary, more particularly the corpus luteum, influences the normal development in pregnancy.—Earl Herrick.

On ovarian regeneration and the oestrous cycle in white rats (A propos de la régénération ovarienne et des modifications périodiques de l'épithélium vaginal chez le rat blanc). Pallot, G., Compt. rend. Soc. de biol. **99**: 1333. 1929.

Total ovariectomy was performed on a dozen animals 60 to 90 days old. In 3 rats oestrus reappeared at the end of 6 months. Two of these showed regenerated ovarian tissue and the other none. Ovarian tissue may regenerate from the ovarian site and oestrus may occur without ovarian tissue being present.—J. C. D.

The functions of the corpus luteum. I. The mechanism of oestrus inhibition. II. The experimental production of placentomata in the mouse. III. The factors concerned in the development of the mammary gland. Parkes, A. S., Proc. Roy. Soc. B. **104**: 171. 1929.

The corpus luteum was shown to be responsible for the oestrus inhibition during lactation in the mouse. Alkaline extracts of the anterior pituitary gland inhibit the oestrus cycle in the mouse due to the formation of lutean tissue. In mice sterilized by x-rays in which there were no organized follicles, the alkaline extracts of the anterior pituitary gland luteinised the remaining tissue which resulted in oestrus inhibition. Placentomata were produced in the mouse during pseudo-pregnancy, lactation, and during the inhibition of oestrus produced by anterior pituitary extract, whereas during normal dioestrus and in x-irradiated females it could not be produced. The luteal phase of pseudo-pregnancy in a non-pregnant rabbit was prolonged to the length of true pregnancy with anterior pituitary extract. This caused the final phase of mammary growth, thus showing that no foetal factor is involved in the complete development of the mammary gland.—E. L.

Notes on testicular grafts in sheep (Expériences et observations relatives a la greefe testiculaire chez le mouton). Porcherel, A., J. Thévenot and Perraud, Compt. rend. Soc. de biol. **99:** 1752. 1928.

Grafting testicular tissue from one variety of sheep into another produced changes in length and weight of wool. This is a possible method of improving the yield from inferior varieties of sheep.—J. C. D.

Influence of sex hormones (male) on the basal metabolism in dogs (Influence des hormones sexuelles [testiculaires] sur le métabolisme basal chez les animaux). Ptaszek, L., Compt. rend. Soc. de biol. **99:** 929. 1928.

Following castration, dogs show a fall in basal metabolism. After about three weeks there is a rise to the normal rate, followed six weeks later by a steady fall to about 65 per cent of the normal rate. This persists but can be temporarily brought back to approximately normal by subcutaneous injections of testicular extract.—J. C. D.

Some interrelations of sexuality, reproduction and internal secretion. Riddle, O., J. A. M. A. **92:** 943. 1929. Abst., A. M. A.

In a study of some interrelations of sexuality, reproduction and internal secretion, Riddle asserts that it is now becoming clear that the specific conditions under which genetic factor operates and develops have an equal value with the genetic factors in the determination of anything that can be called heredity. The factors distributed by germ cells set limits to the nature and appearance of adult characteristics; so do specific conditions. The matter of the control of any characteristics can be approached from either of these two sides. Many different studies during the last decades have helped to prepare the way for this new point of view. But the complete control and reversal of sex in several forms—with its implication of the theoretical possibility of its control everywhere—together with the probable identification of the particular and specific condition (metabolic rate) which here completely overrides the influence of the genetic factor—these events have adequately demonstrated the possibility of making either of many different types of individual out of identical germinal material. Heredity is controlled whenever and wherever development is controlled. Medical science will, for example, doubtless soon be provided with a relatively pure preparation of a hormone of the anterior pituitary with which the infant can be made sexually mature, as has been done already in the rat, mouse and bird. Of course, this agent will not be used precisely thus, but the advent of this specific agent sharply illustrates one type of specific condition with which one can overcome the might of heredity; and future research is sure to provide this and other types in such variety as will bring to medicine a new kind of beneficent power.

Ovarian sarcoma in a child associated with sexual precocity. Southam, A. H., Brit. M. J. **1:** 661. 1928.

Malignant tumor of the ovary in subjects under 10 years of age is remarkably rare. The author reports the case of a girl who, at the age of 2 years and 10 months, had some vaginal hemorrhage lasting three days. Shortly after this a swelling was noticed in the abdomen. A firm, rounded, and freely mobile mass the size of a cricket ball was felt rather to the right of the midline and below the umbilicus. A second vaginal hemorrhage occurred twenty-eight days after the previous period. There was distinct enlargement of both breasts, conforming to the adult female type, and in addition there was a marked development of the pubic hair. The tumor of the right ovary and the right Fallopian tube were removed intact. There were no evidences of metastases. The uterus appeared large for the child's age; the left tube and ovary were normal. The tumor weighed 225 grams. Microscopically, it had the structure of a small, round-celled sarcoma in which there were numerous areas of hemorrhage. There were no remnants of ovarian tissue present. Since operation, two and a half years before, the breasts decreased in size, no further menstruation occurred, and the pubic hair fell out. There has been no evidence of recurrence or metastases.—H. L.

The biological actions of the female sex hormone (Ueber die biologischen Wirkungen des weiblichen Sexualhormons). Steinach, E., M. Dohrn, W. Schoeller, W. Hohlweg and W. Faure, Arch f. d. ges. Physiol. **219**: 306. 1928.

A concentrated placental extract has been prepared, equivalent to 50,000 mouse units per gm., and from it an aqueous solution can be made containing 500 mouse units per gm. Details of the preparation are not given in this paper. The increased tissue circulation in the mammary apparatus caused by administering this endocrine preparation is due to lowering of tonus in the peripheral vessel walls. The areola and mamilla of the albino guinea-pig are especially suited to test such preparations. The mammary apparatus of the normal virgin female is developed at about 17 weeks. It can be produced in infantile castrates after three weeks' treatment with the endocrine preparation (at the age of 7 weeks). The hyperemia is visible at the third day of treatment and can be employed as a biological test for the potency of the hormone. Histological effects on mammae and uterus are described.—A. T. C.

The changes in the ovaries and other organs of animals injected with various ovarian substances. Zerada, M., Japan M. World, **7**: 233. 1927.

Follicular fluid and autolysates of corpus luteum and interstitial gland were injected intraperitoneally into adult female rats. All of the materials injected caused a degeneration of the interstitial gland of the ovary, and interfered with the normal development of follicles. Mature follicles were caused to rupture, and immature ones to develop into cystic follicles. The ovaries of young animals were but little influenced by the autolysates and follicular fluid.
—M. O. L.

Concerning the primateship of the ovum (Ueber das Primat der Eizelle). Westman, A., Acta obst. gynec. Scandinav. **1**: 166. 1928.

Previous theoretical considerations of other authors are discussed with reference to the possibility that ova in transit might influence the development of corpora lutea and corresponding changes in the endometrium. The author has been able to eliminate all influence exerted on the experimental animal by the ova cast off at the time of follicle rupture by doing bilateral salpingectomy on rabbits when all ova are located in the tube on their way to the uterus. In spite of this procedure the corpora lutea as well as the uterine mucous membrane have, anatomically, passed through exactly the same cyclical development as that found in so-called pseudo-pregnancy. The experiments show that the development and function of the corpus luteum are not conditioned by products of absorption from ova liberated from the follicles. Four illustrative experiments are cited. The experiments were carefully controlled. The results seem conclusive.—J. P. P.

Histology of ectopic testes. Interstitial tissue and secretory phenomena (Histologie du testicule ectopique. Tissu interstitiel. Phénomènes sécrétoires). de Winiwarter, H., Compt. rend. Soc. de biol. **99**: 645. 1928.

Two cases, of subjects 23 and 40 years old, are described. There was atrophy of the interstitial tissue in both cases.—J. C. D.

Constipation treated with pituitrin. Ambrose, C. D., Pennsylvania M. J. **32**: 428. 1929.

This is a brief discussion, with two illustrative cases, on the use of pituitrin in intestinal sluggishness. In comparison with eserin it may be said that pituitrin is more prompt and violent, while eserin presents an effect of much longer duration.—I. B.

Hypophyseal "Geographical skull" (Ueber hypophysaren Landkartenschadel). Brehme, T., Ztschr. f. Kinderh. **46**: 401. 1928.

The present case is in a boy of 4½ years who, following a mild trauma, presented softening of the skull bones and symptoms of diabetes insipidus—an increased thirst, increased urine output and a urine with a low specific gravity

and a diminution in NaCl excretion. The administration of pituitrin was followed by a diminution in diuresis, but not in thirst. Novasurol produced a diminution in thirst, an increase in urine NaCl concentration and a lowering of the serum NaCl. The patient was on a salt-free diet.—M. B. G.

On the mode of action of certain extracts of anterior lobe of hypophysis (Sur le mode d'action de certains extraits du lobe antérieur d'hypophyse). Brouha, L. and H. Simonnet, Compt. rend. Soc. de biol. **99**: 759. 1928.

Extracts, both acid and alkaline, were injected into rats. One to six doses were given. The onset of oestrous was delayed in young animals and in adults oestrous was suspended. The authors assume that this is due to an accentuation of the effect produced by the corpora lutea.—J. C. D.

The rôle of the anterior pituitary in compensatory ovarian hypertrophy. Engle, E. T., Anat. Rec. **37**: 275. 1928.

Unilaterally ovariectomized and normal mice and rats were given the same number of daily homeotransplants of the fresh anterior lobe. The weights of the ovaries were compared with those in untreated unoperated and untreated ovariectomized litter-mates. The remaining ovary from unilaterally spayed animals which had the same treatment as the unoperated animals was found to weigh approximately twice as much as the combined ovarian weight in the unoperated, treated animals. Variations in ovarian weights of the treated animals occurred due to physiological limits of response of an organ to increased stimuli, as well as to constitutional factors. In the mouse and rat, at least, it is shown that the anterior lobe of the pituitary furnishes the stimulus for both the structural and the functional hypertrophy of the ovary observed in these experiments.—Author's Abst.

The effect of daily transplants of the anterior lobe from gonadectomized rats on immature test animals. Engle, E. T., Am. J. Physiol, **88**: 105. 1929.

The ovarian response of immature mice and rats following the daily transplantation of the fresh anterior hypophyseal lobe taken from gonadectomized rats is significantly greater than the response to anterior lobe transplants from normal animals. There is no sex difference in the biological potency of the glands of gonadectomized donors, and no significant difference as regards the age of the donor at the time of gonadectomy. While the pituitary of the gonadectomized animal is larger than that of the normal, the ovarian response to the former is so great that storage of the gonadal-stimulating factor is thought to occur. These data offer further evidence which points to a gonadal-pituitary "releasing mechanism," the presence of the gonad being the prime factor involved in the release of this hormone from the organ of origin.

—Author's summary.

Impairment of the birth mechanism due to hormones from the anterior hypophysis. Evans, H. M. and Miriam E. Simpson, Proc. Soc. Exper. Biol. & Med. **26**: 595. 1929.

A hormone of the anterior hypophysis (distinct from the growth hormone) which causes precocious maturity in young female rats, also causes growth of lutein tissue in the ovary. This substance also causes interference with the birth mechanism by prolonging pregnancy 2 to 3 days.—M. O. L.

Stimulation of placentoma reaction in virginal endometrium by treatment with anterior hypophyseal hormone. Evans, H. M. and Miriam E. Simpson, Proc. Soc. Exper. Biol. & Med. **26**: 597. 1929.

The anterior hypophyseal hormone which promotes precocious development of the immature ovary has the same stimulating effect on placentoma formation as does the growth hormone. These substances also cause hyperplasia of the mammary apparatus of 24-day-old female rats, before lutein structures were present in the young ovaries.—M. O. L.

Therapeutic experiments with pituitrin in gastric atony of nurslings and infants (Therapeutische Versuche mit Hypophysin bei Magenatonie im Sauglings- und Kindes-alter). Koenigsberger, E. and W. Mansbacher, Ztschr. f. Kinderh. **44**: 265. 1927.

Studies were carried out in cases of chronic gastric atony, habitual vomiting, marked loss of appetite and marked motor insufficiency of the stomach in dystrophic infants and also in cases of acute gastric atony in any type of child with an acute infection. In addition to the hypodermatic administration of pituitrin, the treatment consisted of lavage, rest period and then gradual increase in feeding. The dose of the pituitrin was 1 cc. after meals, following a three-hour rest. Pituitary extract was used because of its action on unstriped muscle. It was found to act as a gastric stimulant in small doses and as a deterrant in large doses. The authors consider it a valuable therapeutic agent in the treatment of gastric atony. If the pituitrin itself is ineffectual, it may be combined with either adrenalin or atropine sulfate, the combination of pituitrin and atropin being found more efficacious. The dosage will at times depend on individual tolerance.—M. B. G.

Histological evidences of colloid absorption directly by the blood vessels of pars anterior of the human hypophysis. Rasmussen, A. T., Quart. J. Exper. Physiol. **17**: 149. 1927.

From the literature, which is reviewed, one is given the impression that the presence of colloid in the blood vessels of the hypophysis is not an uncommon occurrence. As a result of systematic examination of a hundred normal adult hypophyses (mostly males from cases of sudden accidental death) with oil immersion lens, only two showed any evidence of colloid in the blood vessels. Colloid was especially abundant in the blood spaces of the anterior lobe and in the veins of the capsule and of the infundibular stalk in a young, pregnant female. The method by which the colloid entered the blood stream is not evident. This study indicates that colloid is seen in the blood vessels of the hypophysis in only a few per cent of normal cases.—Author's summary.

Suprapituitary tumor (?). Schlesinger, B., Proc. Roy. Soc. Med. (Sec. Dis. Child.) **21**: 217. 1927.

The case described occurred in a girl of 9 years, whose congenitally large head became increasingly more out of proportion to the size of the body. The circumference of the head was 24½ inches. Hydrocephalus and closed fontanelles were present. There was a deep optic neuritis and a double extensor response. Visual fields were peripherally diminished. X-ray examination showed the sella turcica to be much enlarged, deepened and rounded, and the clinoid processes were not visible.—I. B.

The effect of infantile and foetal anterior lobe transplants on infantile gonads (Tierexperimentelle Untersuchungen über die Wirkung infantilen und fetalen Hypophysenvorderlappenhormons auf infantile Keimrüsen). Siegmund, H. and A. Mahnert, München. med. Wchnschr. **75**: 1835. 1928.

The activating influence of the anterior lobe in the gonad is demonstrable by means of transplants from foetal and infantile sources. Anterior lobes from foetal and suckling calves gave positive reactions when implanted into young female mice. Transplants also gave positive results when taken from human foetuses from the fifth or sixth to the tenth lunar month, a gland from a single foetus being transplanted to the test mouse.—E. T. Engle.

Experimental evidence regarding the rôle of the anterior pituitary in the development and regulation of the genital system. Smith, P. E. and E. T. Engle, Am. J. Anat. **40**: 159. 1927.

Daily transplantations of mammalian anterior pituitary tissue induce precocious sexual maturity in female rats and mice at approximately half the age that maturity normally occurs. This precocious maturity is evidenced by the changes in the genital tract characteristic of normal sexual maturity and also by mating. The ovaries weigh considerably more than those of animals ma-

turing normally, having a greatly increased number of normal follicles and corpora. Superovulation is induced, as many as 48 ova occurring in a single tube. The uterine weights equal those of normally maturing animals. Transplants from immature and senile animals are effective. Immature, but not mature, males respond to the transplants. The testes, however, exhibit a lesser response than remaining parts of the genital tract. The transplants act directly on the gonads and through them on the other genital organs. Transplantations of glands other than the anterior pituitary do not hasten sexual development nor have glandular extirpations, except of the gonads, interfered with the effectiveness of pituitary transplantations. The ovaries of adult females show a profound response to the transplants. Cystic follicles occur in adult treated rats. The findings in treated normal animals harmonize with those secured from hypophysectomy and a replacement therapy. It is concluded that a hormone of the anterior pituitary is responsible for follicular development. The bearing of this on the causation of atresia, ovulation, compensatory gonadal hypertrophy and cyclic changes of the genital tract is discussed.—P. E. Smith.

A method for early diagnosis of bitemporal hemianopsia in tumors of the pituitary (Eine Methode zur Frühdiagnose der bitemporalen Hemianopsie bei Hypophysentumoren). Wiesli, P., Schweiz. med. Wchnschr. **58**: 479. 1928.

The author utilizes a modification by Vogt of the Bjerrum method for the delineation of visual fields. Using the Förster, Bjerrum and Vogt methods in a series of cases, he demonstrates that the latter will detect hemianopsias that are not recognized by the others. He regards the method as capable of defining pituitary or other brain tumors in an incipient stage before fluoroscopy yields definite results. Several fields are reproduced and several illustrative case protocols included.—A. W. R.

Acromegaly; amyotrophic lateral sclerosis. Worster-Drought, C., Proc. Roy. Soc. Med. **22**: 1. 1928. (Clin. Sec.)

The patient was a male of 54 years whose chief complaints were headache, weakness, enlargement of the hands and defective vision. The onset about six years ago was associated with unsteadiness of gait, occasional headaches and visual impairment. A year later both hands became enlarged and weak, and later the head was increasing in size. During the past twelve months the headaches became very intense, with increasing drowsiness. The voice too became less clear and there was dysphagia. The pulse rate was 64, blood pressure 100/70, with subnormal temperature. X-ray examination revealed general enlargement and thickening of skull bones with the pituitary not definitely enlarged but irregular in outline. There was a calcified pineal body and a general enlargement of the small bones of the nose. Considerable bony proliferation in the joint between 11th and 12th dorsal vertebrae was observed. Mentally, the patient was lethargic and irritable and exhibited a very poor memory. There was more evidence in favor of acromegaly than of atypical Paget's disease. The other feature of interest was the association, probably accidental, of amyotrophic lateral sclerosis.—I. B.

Two cases of suprapituitary tumor (Adamantinoma). Wyllie, W. G., Proc. Roy. Soc. Med. **22**: 163. 1928. (Sec. of Laryngology.)

The first patient was a girl of ten with a history of headaches, chiefly frontal, shaking of the hands for twelve months, and increasing obesity. There was no visual complaint or increase of thirst or of micturition. Both optic discs showed papillodema. There was tremulousness in walking and in the use of her hands. A skiogram of the skull showed advanced erosion of the sella turcica. The second patient was a girl of 21 who had always been fat but who developed excessive obesity at the age of 15 years. She showed no sexual distrophy. Both discs showed secondary optic atrophy with a slight degree of swelling. There was some restriction of the visual fields, most marked in the temporal veins. A skiogram of the skull showed marked erosion of the sella turcica, with calcification above.—I. B.

Anterior lobe and ovary (Hypophysen Vorderlappen und Ovarium). Zondek, B. and S. Ascheim, Arch. f. Gynäk. **130:** 1. 1927.

The authors attempted to affect the sex organs of mice by implantation of various endocrine tissues. Only implantation of the anterior lobe of the hypophysis gave positive results. A single implant of anterior lobe, taken from the beef or the human of either sex induced sexual maturity in from eighty to one hundred hours in female mice. This hormone acts only on the ovary; the uterine response is dependent upon the ovary.—E. T. Engle.

Ovulation in pregnancy brought about by anterior pituitary hormone (Ovulation in der Gravidität ausgelöst durch Hypophysenvorden lappenhormon). Zondek, B. and S. Ascheim, Endokrinol. **1:** 10. 1928. Abst., Physiol. Absts. **13:** 664.

Under the influence of the active principle of the anterior lobe of the pituitary body the ovary of the pregnant mouse is stimulated. Follicles ripen and burst and ova reach the Fallopian tubes, and in some cases show chromatin filaments in the nucleus. Corpora lutea are formed in the ovary, and sometimes a living foetus in the uterus.

High carbohydrate diet in under-nourished diabetics (Kohlehydrat-mastkuren bei tenterernährten Zucherkranken). Adlersberg, D. and O. Porges, Wien. klin. Wchnschr. **41:** 1298. 1928.

While previously the authors noticed improvement of tolerance of diabetic patients by the use of heavy protein or carbohydrate diets which were poor in fat, now they find as best routine a low fat, high carbohydrate diet, and give at the same time plenty of insulin to get the patient sugar free. The basis for this procedure is the change of a fatty liver of the diabetic into a glycogen-rich liver. The diet used is as follows: 200-250 gm. meat (weighed after cooking), 3 eggs, 50 gm. fat and enough carbohydrates to make up 3000-4000 calories. Any carbohydrate can be used, even sugar. The patient is kept on this diet 2-4 and even more weeks. This is enough insulin to render the patient aglycosuric; during this course the quantity of insulin required decreases rapidly, and the patient gains markedly in weight. After this there usually follows considerable improvement of the patient's tolerance. Thus, for instance, where at first the sugar output was 35 grams and urine acetone one plus, the sugar and acetone disappeared.—H. J. J.

Danger in the postoperative use of insulin. Andrews, E. and K. Reuterskiold, Surg. Gynec. Obst. **47:** 665. 1928.

In postoperative acidosis and dehydrated conditions glucose and water are needed, but insulin is contra-indicated.—A. T. C.

Case of fatty atrophy following insulin injections. Awrounin, H., Proc. Roy. Soc. Med. **22:** 156. 1928. (Clin. Sec.)

A female aged 56 years had suffered from diabetes mellitus for 15 years. Her urine had been intermittently sugar free, but she did not keep to a strict dietary. Insulin therapy was begun in March, 1927, 20 units twice daily being injected into the arms, more or less in the same area each time. A year later she noticed a dimpling of the arms in the injection area. An examination of the well covered arms showed a deep depressed area on each side at the point of injection below the insertion of the deltoid, where the subcutaneous fat seemed to have entirely disappeared; skin and underlying muscles appeared perfectly normal and were not adherent; the function of the arm was not impaired. The thighs showed an early stage of same lesion.—I. B.

Spontaneous hypoglycemia (Hypoglycémie spontanée). Azérad, E., Médicine, **9:** 755. 1928.

Numerous cases show the existence of spontaneous hypoglycemia, but its mechanism is not understood.—Author's Abst.

Studies on glycemia and glycosuria in normal and diabetic cases (Recherches sur la glycémie et al glycosurie chez l'homme normal et chez les diabétiques). Bacaloglu, C. and S. Strugariu, Compt. rend. Soc. de biol. **99**: 1175. 1929.

There were 1.075 grams of sugar per 1000 cc. of blood in normals. The output of sugar in the urine was 40 to 85 mgm. per day. There was no close agreement between blood sugar and sugar in the urine in either normals or diabetics.—J. C. D.

Treatment of diabetes with special reference to accessory forms of treatment. Bartlett, W. M., Ann. Int. Med. **2**: 334. 1928.

This paper is a criticism of the use of myrtillin, synthalin and glukhorment. The efficacy of myrtillin is questioned because it is usually used in mild diabetes, and there may be increased tolerance to carbohydrate which is not due to the treatment. The action of myrtillin is uncertain and unreliable. Synthalin always causes a loss of weight and lowers the blood pressure. Glukhorment owes its action to the synthalin which is added during the process of manufacture.—E. L.

Unusual increase of carbohydrate tolerance in case of juvenile diabetes. Blaisdell, E. R., J. A. M. A. **91**: 960. 1928. Abst., A. M. A.

A child, 11 years of age, showed symptoms of diabetes for only two weeks, went into coma and was saved by large doses of insulin. A few months later she was able to discontinue the insulin on an 1800 calory diet, containing 80 gm. of carbohydrate. After one and a half years she was still sugar-free with a normal blood sugar, without insulin. The disease was apparently of such a short duration when coma occurred that very little destruction had probably taken place in the islands of Langerhans, and a large percentage of their cells were given an opportunity to regenerate.

The use of insulin in an out-patient department. Blotner, H., New England J. Med. **200**: 491. 1929.

This is a presentation of methods for treating diabetics without hospitalization. Forty-eight cases were treated and all except 10 showed satisfactory results.—J. C. D.

The action of insulin on the perfused mammalian liver. Bodo, R. and H. P. Marks, J. Physiol. **65**: 48. 1928.

Improved technic is described for perfusing the liver of a dog with blood from the same dog containing additional dextrose. Insulin in varying doses was added after perfusion was well under way. Portions of liver were removed as desired for determination of glycogen content. In normal, starved and fat-fed animals, glycogen storage was observed in the absence of insulin, but the latter stopped storage or speeded decomposition of glycogen. Adrenalin caused rapid decomposition even after previous administration of insulin. The authors suggest that the isolated liver does not respond as it does when in coöperation with other organs in the whole animal.—C. I. R.

The relation of synthalin to carbohydrate metabolism. Bodo, R. and H. P. Marks, J. Physiol. **65**: 83. 1928.

A study of synthalin administration in rabbits. While insulin does not normally reduce liver glycogen to extreme low levels, synthalin reduces to very low levels so that the liver does not respond to adrenin and shows evidence of toxic effects. A hypoglucemia is produced which is due to neoglycogenesis. In hypoglucemia after insulin there is increased muscle neoglycogenesis, while synthalin causes muscle glycogenolysis. In addition, there is increased blood lactic acid with the respiratory quotient above unity, and a fall in blood pressure, also decreased oxygen consumption.—C. I. R.

Diabetes mellitus in the negro race: A study of one hundred consecutive cases. Bowcock, H. M., South. M. J. **21**: 994. 1928.

Negroes of all degrees of pigmentation are subject to diabetes. Females are more subject to it than males. It appears at an earlier age in adult negroes than in whites. Obesity precedes it frequently. It is usually mild. Lues does not seem to be a predisposing factor.—J. C. D.

Growth studies of children with diabetes mellitus. Boyd, J. D. and M. V. Nelson, Am. J. Dis. Child. **35**: 753. 1928.

This report of five years' observation of diabetic children confirms the results obtained by others and indicates that if uncomplicated diabetes mellitus is adequately controlled, it does not prevent satisfactory growth. Such control implies approximation and maintenance of normal blood sugar values and an adequate diet. The growth response of these carefully regulated diabetic children is greater than that of groups of non-diabetic children. This would suggest that the present concept of the rate of normal development for a healthy child may not equal his optimum, and that this may be better approximated by careful dietary regulation throughout childhood.—M. B. G.

The effect of insulin on acetonuria. Burn, J. H. and A. W. Ling, J. Physiol. **65**: 191. 1928.

Rats were fed a high fat diet and acetonuria determined on 24-hour samples. Previous observations on seasonal variations in ketonuria were confirmed, this being much greater in summer. After insulin, ketonuria was augmented. In winter there was an increased liver neoglycogenesis on a fat diet, without muscle glycogenolysis or increased total urinary nitrogen. Insulin delayed the increased liver neoglycogenesis, which corresponded to the period of augmented ketonuria.—C. I. R.

Case of disappearance of subcutaneous fat following subcutaneous injections of insulin. Carmichael, E. A. (for G. Graham), Proc. Roy. Soc. Med. **21**: 322. 1928.

In a female diabetic of 49 years, the subcutaneous fat over the left shoulder disappeared as the result of insulin injections.—I. B.

Effect of ergotamine on digestive hyperglycemia in normal and diabetic subjects (Influence de l'ergotamine sur l'hyperglycémie alimentaire chez les sujects normaux et chez les diabétiques). Coelho, E. and J. Candido de Oliveira, Compt. rend. Soc. de biol. **99**: 1527. 1928.

Ergotamine fed with a meal reduced the subsequent rise in blood sugar in both normal and diabetic cases. It is poorly tolerated.—J. C. D.

Diabetes in twins. Curtis, W. S., J. A. M. A. **92**: 952. 1929. Abst., A. M. A.

Only seven instances of diabetes in twins are on record, the author asserts. To these he has added six, making a total of thirteen. The existence of diabetes in twins in some cases almost simultaneously points to an hereditary background and offers a good field for the investigation of diabetes as a problem in heredity. When diabetes develops in a twin, one should consider the other potentially diabetic, particularly if the two are homologous, and any undue strain on the carbohydrate metabolism should be guarded against. The recognition of eight twins (four sets) with diabetes in a series of about 6,000 diabetic patients, when compared with the estimated number of twins in such a group, suggests a larger proportion of diabetes in twins than is the case in single individuals.

Effect of insulin on the external secretion of the pancreas in a case with pancreatic fistula (Action de l'insuline sur la sécrétion externe du pancréas dans un cas de fistule pancréatique). Fonseca, F. and C. Trincao, Compt. rend. Soc. de biol. **99**: 1532. 1928.

Following a meal, the amount of pancreatic juice secreted by this patient was increased after insulin. If no meal was taken, insulin did not change the output. In neither instance was the amount of trypsine or of amylase altered by insulin.—J. C. D.

Insulin treatment in severe diabetes mellitus (Zur Insulindauerbehandlung des Diabetes mellitus gravis). Grantenberg, R., Deutsche med. Wchnschr. **51:** 2141. 1928.

The author discusses 3 severe cases of diabetes which have been under close observation for periods varying from 1 to 3 years, and had to be given large doses (above 50 units) of insulin per day. The author points out the difficulty in giving insulin over such long periods of time. Patients are usually not willing to take more than 3 doses per day; if insulin has to be given in large single doses the danger of hypoglycemia presents itself. He therefore advises the use of opiates. He emphasizes strongly that to properly determine the patient's condition, more than just the fasting blood sugar should be taken during the day in order to get a definite idea as to what is the state of the blood sugar level during the rest of the day.—H. J. J.

Latent tolerance in diabetes mellitus. A study of the effect of high sugar diets with insulin on controlled diabetics. Gibson, R. B., J. Lab. & Clin. Med. **14:** 597. 1929.

Diabetes controlled on maintenance diets with a fatty acid, potential glucose ratio of 1.5 and the required insulin dosage have shown a remarkable improvement in tolerance following two or three days of high sugar ingestion with increased insulin. Successive periods of high sugar diet at intervals of four or five days result usually in a progressive increase in tolerance until dietary management without insulin may suffice to control the diabetes, especially in young individuals. Two mild diabetics, previously controlled, continued to improve in tolerance without interruption of the high sugar diet except for substitutions and additions until a diet of general character was attained.—Author's Abst.

Contribution to knowledge of insulin production (Beiträge zur Kenntnis der Regulation der Insulinproduktion). Grafe, E. and F. Meythaler, Arch. f. Exper. Path. u. Pharm. **136:** 360. 1928.

Previous investigations have shown that dextrose is an adequate stimulus for insulin production, and that this property belongs to all common carbohydrates and appears to be independent of the optical activity. This paper reports investigations of insulin producing activity of split products and carbohydrate-like substances. Hexosanes, glucosamin, oxalic acid, glycuronic acid and oxanthain all exercise a similar influence in stimulating insulin secretion. The action seems to depend on the presence of intact aldehyde and ketone groups.—C. I. R.

Diabetes and hyperthyroidism. Joslin, E. P. and F. H. Lahey, Am. J. M. Sc. **176:** 1. 1928.

The authors report a series of 500 cases of thyroid disease in which they found 38.6 per cent glycosurias in 228 cases of primary hyperthyroidism and 27.7 per cent in 83 cases of adenomatous goiter with secondary hyperthyroidism and 14.8 per cent in 189 cases of non-toxic goiter. They found glycosuria in 13.6 per cent of non-diabetic and non-thyroid surgical patients, and 16 per cent glycosurias in 100 cases of diseases of the gall bladder. A certain degree of hyperglycemia in hyperthyroidism is often found which presents a problem for the differential diagnosis of what one should call diabetes in this group of cases, and thus the authors adopted the standard of a fasting blood sugar of 150 mgm. per 100 cc. (in hyperthyroids) or 200 or more postprandial in addition to glycosuria. According to this standard in the group studied, 75 cases were classified as diabetics. In primary hyperthyroidism 82.1 per cent of 23 cases, and in secondary hyperthyroidism 5 of 8 cases showed hyperthyroidism preceding diabetes. The incidence of hyperthyroidism in diabetes was 1.52 per cent and 2.5 per cent in primary hyperthyroidism with diabetes, and 4.3 per cent in secondary hyperthyroidism with diabetes. The incidence of primary hyperthyroidism in 4917 cases of true diabetes was 0.87 per cent and of secondary hyperthyroidism 0.57 per cent. The authors conclude that surgery greatly ameliorates the condition of these patients. For the group of potential

diabetics (not classified in their paper), they advocate careful observation for a period of years. They consider the hyperthyroid patient as somewhat more prone to diabetes than the ordinary individual.—H. J. J.

Diabetic children. Joslin, E. P. and Priscilla White, J. A. M. A. **92:** 143. 1929. Abst., A. M. A.

The authors have made a study of diabetic children and found that in the twenty-two months ending July 1, 1928, the total mortality among 303 diabetic children has been six, or 1 per cent a year. In the six-year period between August, 1922, and July, 1928, the total mortality for 337 diabetic children has been thirty-six, or 2 per cent a year. The incidence of a diabetic heredity in a diabetic child increases with the duration of his disease and the number of his relatives. An inherited predisposition existed in 17 per cent of the patients who died; it has already reached 35 per cent among the living and 44 per cent among those children whose disease is of more than ten years' duration. Perhaps all diabetes in children is hereditary. Coma is still the cause and almost the only cause of the deaths of diabetic children and represents neglect. The present status of diabetic children is good, but the patients in whom the disease is of long duration usually show glycosuria. They mature sexually. Although one-third of the patients remain underweight, this is to be attributed as a rule to lack of close supervision, a pretuberculous state, or the onset of diabetes long before the use of insulin. Cataracts are not known to exist among 298 living diabetic children. Arteriosclerosis has been demonstrated by roentgenograms in five of twenty-nine children whose disease is of five years' duration or more. Only one of these five children had been on a high carbohydrate diet. Tubercle bacilli have been found in the sputum of one patient; evident pulmonary tuberculosis was present in two cases, and the chest conditions were suggestive in sixteen cases. Of the latter, one-half were neglected because they had had diabetic coma. Overheight at the onset of the diabetes has been demonstrated as varying from 2 7/10 inches on the average for the first series of 100 cases reckoned to the nearest three months to 1 8/10 inches for the second series of fifty-two cases reckoned to the nearest year, or 2 2/10 inches to the nearest three months. Diabetic children resist all types of infections with proper adjustment of diet and insulin. Confusion between the diagnosis of coma and appendicitis is easy and serious; if there is doubt, an operation should be performed. The blood cholesterol of diabetic children is now below rather than above normal. Cholesterol is a true index of the other lipoids. Insulin reactions are distressing but almost never fatal; they interefere with the ideals of treatment but are far less frequent than one would expect because of the inherent honesty of childhood. A child with glycosuria, once carefully diagnosed as being nondiabetic, thus far appears to conform to that diagnosis in the vast majority of instances.

Insulin and adrenin action on the blood sugar during the digestion period in experiments on angiotomised dogs (Insulin- und Adrenalinwirkung auf den Blutzucker während der Verdauungsperiode nach Versuchen an angioostomierten Hunden). Kotschneff, Nina, Arch. f. d. ges. Physiol. **220:** 628. 1928.

After a meal and injection of 1.5 cc. of a 1:1000 adrenin solution no alimentary hypoglycemia was observed. After injection of 20 to 40 units of insulin a similar result was obtained. After meat feeding under normal conditions equal sugar values were found for blood from different veins. Intravenous injection of insulin results in marked retention of glucose by the kidneys, so that the ensuing hypoglycemia is of kidney origin. After a carbohydrate meal and insulin injection there is decreased absorption from the intestines and increased retention by the kidneys. After intravenous adrenalin injection and a meat meal there is, with marked sugar mobilization from the liver, no retention by intestines or muscles, but only by the kidneys.—A. T. C.

Studies of an insulin-resistant diabetic. Lawrence, R. D., Quart. J. Med **12:** 359. 1928.

With the possible exception of cases moribund in coma no well authenticated case is on record in which insulin in large doses has had no effect in lowering the blood sugar of the patient. Cases resistant to insulin are only

relatively and not absolutely refractory. These can usually be accounted for by the following factors which antagonize insulin action: (1) Concurrent infections and sepsis. (2) Overactivity of the thyroid, pituitary, and suprarenal glands, physiological antagonists to insulin. (3) Inefficient treatment of severe cases with high or imperfectly controlled diets and insufficient insulin. (4) Liver disease, which may upon close study be included in the third category. The case reported, as far as can be ascertained, falls into none of these categories. The case is one of a young diabetic man. Diabetes was severe from the onset in 1925, but was controlled by 40 units of insulin daily and a diet of 35 grams C, 38 grams P, and 83 grams F. The fall in blood sugar after insulin was normal at this time. A year later he required 100 units on the same diet, and six months later he was excreting 5 to 10 grams of sugar on a diet of 60 grams C, 80 grams P, and 150 grams F, with 220 units of insulin. When insulin was omitted he went into coma. None of the usual factors enumerated above were present in this case. Blood sugar studies showed features quite different from the ordinary severe diabetic. His blood sugar was lowest after a night's fast. When carbohydrate was given his blood sugar rose in spite of the large doses of insulin. This was not due to delayed insulin action or lack of absorption, because insulin, given in the fasting condition, reduced the blood sugar at the usual rate, though to a less degree than in a "normal" diabetic. The author concludes that in this case insulin cannot deal with ingested carbohydrates in the usual way, by storing it as glycogen. Although it did have its other action of checking the new formation of sugar and ketones from endogenous protein and fat, and that a factor other than insulin is lacking, perhaps some coenzyme which is necessary to the usual action in forming glycogen.—P. H. Charlton.

The insulin treatment of diabetic coma. Leake, W. H., California & Western Med. **26**: 475. 1927.

Basing his views on a study of 53 cases of diabetic coma, the author arrives at the following conclusions: The symptoms of approaching diabetic coma are often misleading. Abdominal pain, nausea, vomiting, fever and leukocytosis, especially in children, may lead to the diagnosis of an acute abdominal condition. Decreased intraocular tension is a very important sign in the diagnosis of diabetic coma. It is practically always present. In addition to the liberal use of insulin, buffered with carbohydrate, the treatment of diabetic coma consists mainly in forcing fluids, warmth, elmination, and stimulation with caffein sodium benzoate and digitalis. Not more than 25 gm. of sodium bicarbonate should be administered daily. Diabetics develop coma rapidly when deprived of insulin. Coma in these individuals is apparently more resistant to insulin therapy than in patients who have not received insulin previously. In the hands of those familiar with its action insulin often saves lives, but if used carelessly the results may prove disastrous.—I. B.

Two cases of diabetes treated by synthalin. Linder, G. C. (for F. R. Fraser), Proc. Roy. Soc. Med. **21**: 324. 1928.

This report presents one successful and another unsuccessful result from the use of synthalin in the treatment of diabetes mellitus.—I. B.

Increased effect of insulin in experimental cases of impermeable kidney (Augmentation de l'action de l'insuline dans l'imperméabilité rénale expérimentale). Loeper, M., A. Lemaire and J. Tonnet, Compt. rend. Soc. de biol. **99**: 19. 1928.

Action of insulin in cases of impermeable kidney in man (L'action de l'insuline dans l'imperméabilité rénale de l'homme). Loeper, M., J. Ravier and J. Tonnet, Compt. rend. Soc. de biol. **99**: 20. 1928.

In rabbits, ligation of the ureters prolongs and accentuates the effects of insulin. Similar results follow in human cases where there is decreased renal permeability.—J. C. D.

Insulin treatment of scleroderma. Michaëlis, O., Bruxelles-Medical, **9**: 560. 1929. Abst., J. A. M. A. **92**: 1716.

Michaëlis reports a case of generalized scleroderma in a woman, aged 30. After many kinds of treatment (including antisyphilitic treatment and opotherapy with various endocrine gland extracts) had proved of no avail, the author decided to try insulin, because the patient had had attacks of local asphyxia of the fingers (Raynaud's disease). Amelioration of the condition was observed after the first few injections, and it progressed steadily notwithstanding many recurrences of the symptoms. In one year the patient received 4,970 units of various brands of insulin, combined with fifty ultra-violet irradiations which were given during the last two months of treatment. This improvement continued after the treatment had been stopped, so that the author anticipates a complete cure. The skin became soft and could be raised in folds on almost the whole body, and the patient could make many movements that had been limited or abolished before the treatment.

The chronaxie of nerves and muscles in insulinized frogs (La chronaxie des nerfs et des muscles de la Grenouille insulinsée). Olmsted, J. M. D., Arch. Int. Physiol. **30**: 202. 1928.

Since in insulin overdosage the convulsions produced are similar to those caused by strychnine injection, this author investigated the excitability of the gastrocnemius muscles of insulinized frogs. The irritability of the heart was also measured. There was no change in the irritability of either. The excitability of the sciatic nerve does not change, but it is possible that the medulla is more irritable at the time of the convulsions. During the interval between convulsions the excitability is the same as normal.—E. L.

The dietetic management of the diabetic in the doctor's office. Olmsted, W. H., Ann. Int. Med. **2**: 325. 1928.

The reasons as set forth by the author for measuring the food is that if insulin and diet are not balanced, the urine will contain sugar or the patient will experience symptoms of hypoglycemia. Secondly, definite improvement in tolerance will not follow unless the urine is kept sugar-free. In diabetic education some patients are taught to weigh or measure food by the metric system. The author has classified diabetics into three groups. The first is a group having practically no education, the second are mild diabetics with some education, and the third are intelligent diabetics, very severe cases and young patients. This last group should be taught the metric system. The method of education of the second group (mild cases) is fully considered. Food is measured by methods of the modern housewife; i. e., cupful, tablespoonful and teaspoonful. The standard half-pint measuring cup is used for measuring food. The unit of carbohydrate measurement is the level teaspoonful or 4 grams. There is included, a table which gives the amount of sugar in teaspoonfuls according to cupfuls of foods. The patient chooses foods available in such amounts as will make the number of teaspoonfuls of sugar allowed. A table of albuminous foods is also included. The unit of fat is taken as the square of butter made by cutting off one-half inch from the quarter pound package. This represents about 10 grams of fat. The table gives equivalents of fat containing foods in squares of butter.—E. L.

The pathology of diabetes in young adults. Page, J. H. and S. Warren, New England J. Med. **200**: 766. 1929.

The findings in 11 patients, from 12 to 33 years of age, emphasized (1) the slight and variable changes in the pancreas, and (2) the very striking evidence of disturbance of lipoid metabolism as shown by extensive atherosclerosis.
—J. C. D.

An unusual case of diabetes and gout. Rabinowitch, I. M., Canada M. A. J. **19**: 682. 1928.

A patient who had had typical attacks of gout five or six times a year for 10 years was admitted to a hospital with diabetes severe enough to demand insulin. Insulin treatment precipitated attacks of gout. Synthalin treatment

was attempted and initially gave rise to cramps and diarrhoea. There being no evidence of liver damage, the synthalin treatment was persisted in, and for fifteen months the urine has been kept sugar-free and the blood sugar practically normal without the use of insulin. High plasma cholesterol persists, indicating that unlike insulin, synathalin has no effect on the metabolism of cholesterol. A second case of diabetes with gout did not exhibit the anomaly, much larger doses of insulin producing no attacks of gout.—A. T. C.

The cholesterol content of blood plasma in diabetes mellitus. Rabinowitch, I. M., Arch. Int. Med. **43**: 370. 1929.

Plasma cholesterol affords a reliable index to the true progress of the diabetic patient. Because of the simplicity with which the test can be carried out, estimation of the plasma cholesterol should form part of the routine management in diabetes. As with all laboratory tests, in the interpretation of results obtained consideration should be given to other conditions which might lead to high values. These include jaundice, cholecystitis, pregnancy, nephrosis, etc.—Author's summary.

The action of insulin on regeneration. The biological rôle of potassium and calcium ions in the process (Die Wirkung des Insulins auf die Regeneration. Die biologische Rolle der K- und Ca-Ionen bei diesem Vorgange). Schazillo, B. A. and M. Je. Ksendsowsky, Arch. f. d. ges. Physiol. **220**: 774. 1928.

Insulin assists bone regeneration. Injection of isotonic KCl solution subcutaneously inhibits the insulin action, but isotonic calcium chloride solution favors it.—A. T. C.

Diabetes. Late results of insulin treatment. Treatment with synthalin. Strouse, S. and B. Y. Glassberg, M. Clin. North America, **12**: 79. 1928.

A brief review of the subject, with nine illustrative cases, is given. The difficulties encountered by the physician when the patient evinces little or no coöperation are stressed. Generally speaking, the authors found synthalin unsatisfactory. Aside from such symptoms as nausea, vomiting and abdominal pain, the effects in the control of carbohydrate metabolism do not compare with those following the use of insulin.—I. B.

Pancreatic cyst with diabetes. Timme, A. R., California & West. Med. **26**: 349. 1927.

This is a report of a case of pancreatic cyst with papilloma of the wall of the cyst possessing some malignant characteristics. The patient was a married woman of 44 whose chief complaint was enlargement of the abdomen and pain and weakness of the legs. The latter proved to be typical neuritis associated with diabetes mellitus. There was a loss of 53 pounds in weight. The patient made an uneventful post-operative recovery and was placed under a diabetic regime of treatment.—I. B.

Diabetes and tuberculosis. Tompkins, R. D., South. M. J. **22**: 143. 1929.

Thirteen cases are briefly considered. In most of these the diabetes was successfully controlled by insulin, but the tuberculosis could not be favorably influenced.—J. C. D.

Note on the action of ergotamine on glycemia (A propos de l'action de l'ergotamine sur la glycémie). Trincao, C., Compt. rend. Soc. de biol. **99**: 1538. 1928.

In three diabetics, when insulin and ergotamine were given together, the reduction in the hyperglycemia following a glucose meal was the same as when insulin alone was used. In a fourth diabetic the reduction was much greater, equal to the reduction produced by ergotamine alone plus that of insulin alone.
—J. C. D.

The rôle of secretin in the regulation of the alkali-reserve of the blood (Zur Frage nach der Rolle des Sekretins bei der Regulierung der Blutalkalireserven). Wolnar, A. O., Arch. f. d. ges. Physiol. **221**: 144. 1928.

Secretin plays a distinct rôle in the regulation of the alkali-reserve of the blood. There is a direct relationship between the variation of alkalinity of the secretin-pancreatic juice and the alkali-content of the blood. Where there is decreased alkali-reserve, at the same time there is a decreased alkalinity of the juice. Artificial increase in the blood alkalinity (by injection of sodium carbonate) increases the amount and degree of alkalinity of the juice.—A. T. C.

Response of the higher nervous centers to hypoglycemia following insulin (Sensibilité des centres nerveux supérieurs a l'hypoglycémie provoquée par injection d'insuline). Zunz, E. and J. LaBarre, Compt. rend. Soc. de biol. **99**: 631. 1928.

Three dogs were used. The head of a dog "B" was isolated from its body, except for the vagii, and supplied with blood from dog A, in which hypoglycemia had been produced by the injection of insulin. The pancreatic vein of B was connected with the jugular of a depancreatized dog, C. All dogs were anaesthetized with chloralose. The hypoglycemia of dog A has little effect. If hyperglycemic blood is substituted, however, it acts through the blood stream on the higher centers of B. These, through the vagii, cause an increased output of insulin from the pancreas of dog B, which is indicated by a fall in the blood sugar of dog C. The higher centers, therefore, respond to changes in blood sugar and may act directly to control it.—J. C. D.

Tumors of the parathyroid glands. Guy, C. C., Surg. Gynec. Obst. **48**: 557. 1929.

Adenomata of the parathyroids are comparatively rare. Apparently benign tumors of years' duration may suddenly take on malignant character. The question of true adenoma formation or of hyperplasia may be difficult to decide in enlargements of the parathyroids. Parathyroid tumors are easily confused with thyroid tumors. Their histological character shows considerable variation. —A. T. C.

Concerning the influence of the hormones of the parathyroid on the liver (Über den Einfluss von Hormon der Epithelkörperchen auf die Leberfunktion). Kim, M. H., Trans. Japanese Pathol. Soc. **18**: 383. 1928.

In parathyroidectomized rabbits dye excretion of the liver is depressed, while the output of foreign proteins is increased. The parathyroids, therefore, have an important influence on liver excretion and on assimilation of foreign proteins.—R. G. H.

The effect of colectomy on the incidence of parathyroid tetany and the blood calcium. Oldberg, E. and E. L. Walsh, Am. J. Physiol. **85**: 531. 1928.

Several series of experiments were performed. In the first series of ten dogs, the colon was removed, and about a week later the parathyroids were removed. In four dogs, tetany was not seen; in three others it was considerably delayed; and in the other three it developed in the usual time. In the second series of ten dogs, the parathyroids were removed; and on the incidence of tetany, the colon was removed. Tetany usually occurred on the second day after parathyroidectomy and again on the second day after colectomy. In the third series of two animals, the parathyroids and colon were removed at one operation. In both animals tetany occurred on the second day after operation. In a fourth series, the blood calcium was followed after colectomy in eight dogs. It was found that an increase in serum calcium occurred. The increase amounted to from 0.8 to 3.0 mgm. per 100 cc. of serum and occurred in from 4 to 7 days, and then declined to normal in about 10 or 12 days. In a fifth series, five dogs were used whose colons were removed and whose parathyroids, about 4 days later when the blood calcium was the highest, were also removed. The fall in blood calcium following the removal of the parathyroids was somewhat slower than in dogs only parathyroidectomized and somewhat higher than

usual at death. It was concluded that (1) when colectomy precedes parathyroidectomy, the onset of tetany is modified; (2) when colectomy succeeds parathyroidectomy, only a transitory depressant action on tetany is noted; (3) and that the removal of the colon of the dog causes in most cases a transitory rise of blood serum calcium of 0.8 to 3.0 mgm. per 100 cc. of serum.—Author's Abst.

The pineal body. Jelliffe, S. E. (Nelson's Loose Leaf Medicine, May, 1928).

This is the most complete condensed review of the literature upon the pineal that has appeared in recent years. The author neglects almost nothing, possibly with the exception of some of Pines' work upon the pineal neural connections, which, however, appeared too late in Russian literature translations or reviews to be included. The general trend of this work is to cast considerable doubt upon the endocrine function of the pineal and to emphasize its neural connections.—Author's Abst.

Dysgenitalism of splenic origin (Le Dysgenitalisme d'Origine Splenique). Radossaviyevitch, A. and A. Kostitch, Rev. franç. d' endocrinol. **7**: 22. 1929.

This is a clinical and experimental study of the relation of the spleen to the female sex glands. The experimental work consisted chiefly of studying the effects of splenectomy on the production of a precocious sex cycle as determined by vaginal smears in the immature white mouse. Splenectomy produced oestrus in 17 of 22 cases. In the remaining five cases the oestrus was delayed. Clinical evidence of an inter-relation between spleen and genital glands is also given.—B. C.

Some sidelights on the thymus vogue. Garland, J., New England J. Med. **200**: 59. 1929.

After an analysis of 1564 autopsy cases, 23 of which showed enlargement of the thymus, the author considers that the present vogue of x-raying for thymus and radiating all cases in which a shadow appears would seem to be unjustified.—J. C. D.

Irradiation of the thymus gland in the treatment of psoriasis. Jamieson, R. C., Arch. Dermat. & Syph. **18**: 109. 1928.

The work reported was similar to that which Foerster reported in 1921, and reviews the reports of European observers who had treated psoriasis by this method. The majority of reports quoted by the author regarded this method of treatment as one which should at least be given a trial, although favorable results could be expected in only a certain variable percentage of cases. The cases reported, 50 in number, were rayed over the thymus area, using 88 kilovolts, 5 milliamperes, skin target distance of 12 inches, a 3 mm. aluminum filter, and an exposure of 3 to 5 minutes, depending on the type of patient. Many of those treated also received thymus extract orally. Ten per cent of the cases were considered to be definitely improved, thirty-four per cent showed temporary improvement, while the remainder were unimproved. The writer believes that irradiation of the thymus gland, either with or without thymus extract internally or by injection, has a certain definite, though possibly small, value in the treatment of psoriasis. It has not produced any harmful effects, but further work will be necessary to improve the technic and standardize the dose of x-ray.—Author's Abst.

The relative sensibility of normal and involuted thymus when exposed to x-ray (Sensibilité comparée aux rayons X d'un thymus normal et d'un thymus involué). Jolly, J. and R. Ferroux, Compt. rend. Soc. de biol. **99**: 718. 1928.

Guinea pigs of various ages were exposed to x-ray under standard conditions. The thymus was removed six hours later and examined. Nuclear pyknosis and other evidence of active response to the x-ray was found, regardless of the degree of involution of the gland or the age of the animal.—J. C. D.

Status lymphaticus. Marine, D., Arch. Path. **5**: 661. 1928. Abst., Arch. Neurol. & Psychiat. **20**: 614.

This article is a comprehensive review of present knowledge of the problem of status lymphaticus. Status lymphaticus may be defined as a constitutional defect, usually congenital (although it may be acquired), dependent on an inadequacy of some function of the suprarenal glands, the sex glands and the autonomic nervous system and associated with lowered resistance to a great variety of non-specific, physical and chemical agents. Anatomically, it is characterized by delayed involution or hyperplasia of the thymus, hypertrophy and hyperplasia of the lymph glands and lymphoid tissue of the various organs, underdevelopment of the chromaffin, gonadal and cardiovascular systems and by certain pecularities of external configuration.—Author's Abst. (abbreviated).

The so-called condition of status thymico-lymphaticus and its relation to the endocrine system (Über den sogenantet Status thymico-lymphaticus und seine Beziehungen zum endokrinen System). Oswald, A., Schweiz. med. Wchnschr. **58**: 1173. 1928.

The criteria for the diagnosis of status thymico-lymphaticus given in this paper are: a pale skin, excessive development of subcutaneous fat pads, hypoplasia of the heart and blood vascular systems, enlargement of the thymus and lymphatic apparatus, and diminished resistance to physical, bacterial, and toxic agents, with a great tendency to sudden death. According to the author, enlargement of the thymus is not the cause of sudden death in cases of status thymico-lymphaticus, but rather reflects a disturbance of the interrelation between the thymus and the other glands of internal secretion. He also believes that the thymus may play a part in the defense mechanism against injurious humoral influences. He then cites the well-known thymus enlargement in Grave's disease, but states that there is no experimental proof of such an interrelation. The well-known enlargement of the thymus and hypertrophy of the lymphatic apparatus that is associated with absence of primary sex organs is also stated as evidence of the relation of the thymus to the other endocrines. The large thymus that is seen in acromegaly he relates to the atrophy of the primary sex glands that occurs in this disease. The most striking relation of the thymus to the other endocrines is seen in its interrelation with the sex glands.—H. L. Jaffe.

The effect of thymus on water and salt regulation (Thymusextrakt und Wassersalzhausalt im fruhen Sauglingsalter). Seckel, S., Ztschr. f. Kinderh. **44**: 473. 1927.

The effect of thymus extract on water elimination was studied in 17 infants up to the age of six months. In the majority of experimental cases there was an incomplete total water excretion, a diminution in renal and extrarenal elimination and an evident NaCl retention. The effect of thymus extract is one of hydremia and may be considered on the basis of a tissue water retention. Secondary effects of thymus extract are a mild bradycardia, dilatation of the circulatory system and an inconstant diminution in the number of leucocytes. The blood sugar remains unchanged. Thymus extract, like the pancreas hormone, stimulates water retention and vasodilatation. Both of these hormones in this respect can be considered as vagus stimulants and as antagonists to the sympathetic action of the adrenal and thyroid hormones. The tissue water retention properties of thymus extract and of insulin permit the therapeutic combination of both of these in the management of infantile dehydration.
—M. B. G.

The condition of thyroxine in the animal organism (Studien über das Verhalten von Thyroxin im tierischen Organismus). Abderhalden, E. and E. Wertheimer, Arch. f. d. ges. Physiol. **221**: 82. 1928.

Muscle tissue shows the greatest uptake of thyroxine. Liver tissue is scarcely affected.—A. T. C.

The fate of the thyroid hormone in the organism of hyperthyroidized mammals (Weiterer Beitrag zur Frage des Schicksals des Schilddrüssenhormons im Organismus hyperthyreoidisierter Säugetiere). Asimoff, G. and M. Lapiner, Arch. f. d. ges. Physiol. **220**: 588. 1928.

Using the axolotl metamorphosis as a test, it is shown that the thyroid hormone can be detected in the blood and urine of a dog after administration of a large dose (100 gm. or more) of desiccated thyroid. It can be detected in the blood from 2 to 20 hours after administration. It leaves the organism more rapidly in mammals than in birds. The maximum excretion in urine is between 6 and 18 hours after administration.—A. T. C.

Heart-block influenced by inspiration in a case of Graves' disease. Bourne, G. (for P. Hartley), Proc. Roy. Soc. Med. **21**: 322. 1928.

An unmarried white female of 34, in 1921, suffered from exophthalmic goiter. Within a year, as the result of medical treatment, she became so well as to be able to resume her occupation as typist. Following a severe attack of influenza in 1927, the syndrome recurred, excepting that the heart rate was 65 per minute. The basal metabolic rate was plus 41 per cent. Electrocadiographic and polygraphic tracing showed the presence of a 2:1 heart-block. The block was completely removed for 45 minutes by ½ cc. of adrenalin. It was not abolished by 1/33 gr. of atropin sulphate subcutaneously. It was increased by pilocarpine nitrate. The author suggests that the phenomenon shows the presence of inspiratory increased accelerator tone, in addition to the decreased vagal tone known to exist.—I. B.

The iodine content of the thyroid of two species of elasmobranchs and one species of teleost. Burwash, Frances M., Contrib. Can. Biol. & Fisheries, **4**: 115. 1929.

The skates **Raia laevis** and **R. erinacea** contain respectively for males an average of 0.031 and 0.025 per cent iodine in desiccated thyroid tissue, and for females 0.048 and 0.049 per cent. Results for the female haddock referred to the whole weight of the fish indicate that its thyroid contains iodine of the same order as those of elasmobranchs, while two analyses for males gave values of a lower order. A hyperplastic condition of the thyroid was noted in two female **R. laevis.** One of these thyroids on analysis showed an iodine content much above normal.—A. T. C.

The vagus and the thyroid (Penumograstrique et appareil thyroïdien). Cardot, H., J. Régnier, D. Santenoise and Vidacovitch, Compt. rend. Soc. de biol. **99**: 64. 1928.

When the vagus of a dog is cut in the neck, there is increased cerebral excitability, due to the activity of the thyroid. The present experiments involved cutting the vagus in various places and showing that the effect on the thyroid was of true vagus origin and not due to the inclusion of sympathetic fibers.—J. C. D.

Roentgen treatment of thyroidal dysfunction. Carulla Riera, V., Revista Medica de Barcelona, **10**: 390. 1928. Abst., J. A. M. A. **92**: 1026. 1929.

Carulla Riera divides patients with hyperthyroidism into three types, the Basedowian, those who have thyro-toxic adenomas, and, finally, the patients with essential hyperthyroidism. Patients in the last group present all the symptoms suggesting that pathogenesis without showing enlargement of the thyroid. In this group and in the basedowian group, roentgen treatment yielded good results. The group with thyro-toxic adenoma is not so amenable to this treatment. Success depends largely on the correct diagnosis. There is no contraindication to the treatment and it is neither dangerous nor troublesome; all the salivary glands, however, must be carefully protected. All the author's patients received rest in the country. As these patients are inclined to be depressed, their environment must be optimistic.

Selective growth of adult plumage in chicks treated with thyroid (Déterminisme thyroïdien de la poussée du plumage adulte chez les poulets). Champy, C. and J. Morita, Compt. rend. Soc. de biol. **99**: 1116. 1929.

Chicks treated with very small doses of thyroid showed changes of certain groups of feathers, notably those of the back of the neck, tail, and area anterior to wing. These feathers showed growth and color resembling the adult type.
—J. C. D.

Further observations on tryptophan and the thyroid gland. Chang, H. C. and W. C. Ma, Chinese J. Physiol. **2**: 329. 1928.

Experimental evidence at hand shows that the morphology of the thyroid glands of albino rats varies with body weight. The thyroids of unmated male and female albino rats of the same age may be different as their growth rates are different. The morphological evidence indicates that the heavier male has a better functioning thyroid. Litter mates of the same sex, kept under identical conditions, may show different body weights with different thyroid pictures. It is probable that the atrophic thyroid is responsible for the stunted growth, but the possibility of other endocrine glands should be ruled out. The mitochondria vary in number and shape according to the functional state of the thyroid glands. Numerous long filaments are found in the normal thyroids, while scanty rod or granulated forms are present in the atrophic glands. Tryptophan apparently has no specific morphological influence on the thyroid gland. The work thus far done on tryptophan by different investigators shows that it is not related to the thyroid hormone.—Authors' Summary.

The complications of thyroidectomy. Cox, H. H., Illinois M. J. **54**: 157. 1928.

The author believes that the general mortality incident to thyroidectomy in thyrotoxicosis is much greater than is stated in the representative clinics. Thyroidectomy is fraught with dangers both during the operation and after. A thorough knowledge of the anatomy of the thyroid and its related structures is essential in the interests of safety. Hemorrhage is probably the most frequent accident encountered during the operation. Injury to the recurrent laryngeal nerve is next in order. The next most serious danger to be avoided is collapse of the trachea. Another common complication is tetany due to injury or removal of the parathyroid bodies. In the author's series of cases, parathyroid damage was demonstrated in 14 per cent; most were latent and transient.—I. B.

Metastasis to thyroid gland from endothelial myeloma of bone; rapid regression resulting from roentgen-ray treatment. Craver, L. F., J. Lab. & Clin. Med. **9**: 878. 1927.

The case reported was that of a white man of thirty, who, prior to coming under the observation of the author, had an arm amputated for supposed periosteal sarcoma in one hospital, and an operation on the thyroid in another hospital for supposed carcinoma of this organ. He now presented a large mediastinal tumor, said to be an extension of the thyroid carcinoma. Examination of pathological sections from both hospitals revealed the fact that the patient was suffering from endothelial myeloma of the humerus, with metastasis to the thyroid. The remarkable radiosensitiveness of endothelial myeloma was exemplified by the rapid regression of the mediastinal mass under roentgen-ray treatment. The patient has now been apparently well for three months, although rapid recurrence is to be expected in this type of tumor.—I. B.

Factors determining the end-results of thyroidectomy for hyperthyroidism. Crile, G. W., South. M. J. **22**: 137. 1929.

On a basis of extensive personal experience, Crile concludes that the symptoms of hyperthyroidism and of adrenalism are the same. Both cause increased heart action and increased pulse pressure, dilation of the vessels of the skin and sweating, dilatation of the pupils, increased metabolism, hyperglycemia, gastrointestinal disturbances, and nerve activation. The injection of adrenalin in a patient with hyperthyroidism produces an exaggeration of the symptoms of hyperthyroidism. This observation has been confirmed by experimental evi-

dence. The function of the thyroid gland is a building-up or changing mechanism; that of the adrenals is a discharge mechanism. Probably the only causes of thyroid crises are those factors which cause an increased output of adrenalin. These factors are: Pain, emotional excitation, foreign proteins, auto-intoxication, wound secretion, focal infection, infectious diseases, asphyxia, inhalation anesthesia, hemorrhage, the injection of adrenalin. Each causes an increased output of adrenalin. It follows that any plan of hospital and operative management and any post-operative regimen whereby these factors can be avoided must have a direct influence upon, must promote both the immediate and the remote results of thyroidectomy for hyperthyroidism.—R. G. H.

The influence of thyroid preparations on the cardiac and vascular nerves. Dreyere, H., Quart. J. Exper. Physiol. **19**: 61. 1928.

All experimental conditions were carefully controlled and checked. Thyroid extract causes a fall in blood pressure in cats and dogs, but not in rabbits. There was no specific or constant effect on the irritability of cardiac nerves. Thyroxin had no effect on blood pressure or cardiac nerve irritability in acute experiments.—C. I. R.

Relationship of hyperthyroidism to joint conditions. Duncan, W. S., J. A. M. A. **91**: 1779. 1928. Abst., A. M. A.

A man, aged 55, complained of nervousness, weakness, loss of weight and a rapid heart. He did not notice a goiter, but on clinical examination he manifested the classic signs of a very marked hyperthyroidism. While in the hospital a severe neuritis, so called, developed in the right shoulder and arm, which proved to be extremely incapacitating and persistent during the following 3 months of rest at home. Within this period a similar condition arose in the left upper extremity. Three weeks following admission complete thyroidectomy was performed, the wound being left open for twenty-four hours and then being closed. Section of tissues showed an adenomatous goiter. The patient was discharged on the fifth day after operation. The striking features in the patient's condition were the persistent and progressive periarticlular changes involving the joints noted, which completely failed to respond to any of the recognized physical measures and forms of medication up to the time the thyroidectomy was performed. Within from forty-eight to seventy-two hours following operation the severity of the pain in the extremities had lessened almost miraculously. Three weeks following his discharge the arthritis in his right hand and shoulder was gradually giving way; no sedatives had been required since his discharge; there was yet considerable stiffness in the shoulder joint and in the right hand, but he felt confident that this would gradually disappear. Six months later there was some stiffness of his right forearm and knuckles, but the shoulders were completely normal. Similar results were manifested in the case of a woman. Whether or not the thyroid gland itself is the prime factor in the production of these cases one cannot state positively, although it seems most logical that this is another manifestation of a condition that is comparable to a toxemia which gives rise to such widespread changes throughout the body. Of the group of cases observed by Duncan, 64 per cent were females, a fact which accords with the experience of other persons particularly interested in an analysis of the so-called endocrine arthritides. In regard to the influence of the menstrual function in these cases, the majority of the patients had passed the menopause. It was noteworthy in these cases that the first signs of disease of the joints appeared at the time the hyperthyroidism was at its height and that the severity and extent of the joint involvement appeared to be in direct proportion to the severity of the hyperthyroidism. More than 80 per cent showed the earliest manifestation to be in the shoulders, and of this group over half had bilateral involvement. The author cannot agree with other observers that in this particular form of endocrine disease the joint changes are always symmetrical. Next in order of frequency of involvement were noted the knees; the metacarpophalangeal and interphalangeal joints of the hands were almost as frequently affected; next the feet and lumbar spine, and hip joints in order of frequency. In approximately half of these cases the joint involvement was multiple, with almost invariably the onset occurring in the shoulders with rapid or gradual involvement of other articulations. The degree of joint change is dependent on the severity of the hyperthyroidism and

the duration of the disability prior to the institution of radical treatment. The onset of the joint condition appeared to coincide with the height of the thyroid disease, even mild trauma in two instances acting as an inducing agent.

Anesthesia in thyroid surgery. Dunhill, T. P., Proc. Roy. Soc. Med. **21**: 345. 1928.

Thyroidectomy is an operation that should not be prolonged more than is absolutely necessary, therefore anesthesia that makes it easier for the surgeon is a direct gain to the patient. An operation on the thyroid gland will almost always cause increased secretion in the trachea which will interfere with the patient's expulsive efforts. Therefore the anesthetist should not be asked to give an anesthetic until the buccal and pharyngeal cavities are clean. Nor should an anesthetist be expected to induce anesthesia in a patient with great mental unrest or a very high pulse rate, since thyroidectomy is not an emergency operation.—I. B.

Treatment of exophthalmic goiter. Fenger, M., Ugesk. f. Laeger, **90**: 623. 1928. Abst., J. A. M. A. **91**: 844.

Fenger and his associates studied 543 cases of exophthalmic goiter, 362 treated medically and observed from 3 to 14 years, and 181 cases treated surgically and observed from 2 to 14 years. Their main conclusion is expressed thus: If of 200 cases of pronounced typical exophthalmic goiter, 100 are treated surgically and 100 given medical treatment, the surgeon will cure about twice as many of his hundred cases as the internist of his 100; roentgen-ray treatment does not materially affect this result.

Antitryptic titre in pregnancy and in hyperthyroidism. Flexner, L. B., J. Berkson, H. Winters and I. Wolman, Proc. Soc. Exper. Biol. & Med. **26**: 592. 1920.

With the idea that the antitryptic substances in blood serum may affect catabolism, determinations of the titre of these substances were made in cases of pregnancy and toxic hyperthyroidism, in which metabolic changes are prominent. Determinations of the titre in blood of 159 pregnant women were made. There was a progressive rise of the antitryptic titre from conception until about 170 days before parturition. Twenty-five patients with hyperthyroidism and increased basal metabolic rates showed an antitryptic titre above normal. About two thirds had a titre between plus 12 and plus 52 per cent.—M. O. L.

The chemistry of the oestrus producing hormones. Funk, C., Proc. Soc. Exper. Biol. & Med. **26**: 568. 1929.

The author believes the oestrus producing hormone of the ovary to be a phenol or alcohol forming, easily soluble salt with strong alkalies. These salts are fairly soluble in ether.—M. O. L.

The male hormone. II. Funk, C., B. Harrow and A. Lejwa, Proc. Soc. Biol. & Med. **26**: 569. 1929.

A testicular extract made by the authors showed chemical properties somewhat similar to the oestrus producing hormones of the ovary. The material was extracted from the urine of young men. The test of potency and the method of assay used were the effect on the growth of the comb in castrated cocks.
—M. O. L.

Iodin content in the thyroid of Uruguayan cattle (Teneur en iode des glandes thyroides des bovidés de l'Uruguay). Goslino, A. E., and M. I. Ferrero, Compt. rend. Soc. de biol. **99**: 1446. 1929.

The iodine content varied from .35 grams to .52 grams per 100 grams of dried gland. It was higher in cows than in steers. There were no marked seasonal variations.—J. C. D.

The thyrotoxic symptom complex in chorea minor (Der thyreotoxische Symptomenkomplex bei Chorea minor). Kundratitz, K., Ztschr. f. Kinderh. **43**: 659. 1927.

The author believes that dysthyroidism is of etiological importance in chorea minor and that many of the symptoms present can be explained on a thyrotoxic basis. The appearance of the eyes is similar to that found in thyrotoxicosis. Graefs and Moebius' signs were found in only one case. The skin in chorea shows a vasolability expressed in blushing and in dermographia. Paradoxical breathing as described by Czerny (pulling in or flattening of the thorax on inspiration) is present in both chorea minor and hyperthyroidism. The blood picture in both chorea and hyperthyroidism consists of lyphocytosis and occasionally an eosinophilia. The endocarditis in chorea may be considered as due to a thyrotoxicosis instead of to a rheumatic infection. The psychic changes, such as change of voice, irritability, restlessness and lack of concentration are similar to those found in Basedow's disease. Serejski's observation of a local regional vegetative reflex in hyperthyroidism was found in two of the children with chorea. Sweating and a flushing in thyroid region is obtained on the injection of pilocarpin. Both in cases of Basedow's disease and chorea a lowered sugar tolerance, an increased B. M. R. and increased temperature are shown. The Abderhalden test for thyroid dyscrasia was present in 81 per cent of the cases in the author's series of chorea minor. Other conditions, such as encephalitis, nephritis, impetigo, tetany and pleurisy, gave a lower percentage. The author concludes that part of the symptomatology of a fully developed case of chorea can be considered from a hyperthyroid basis. Two cases which were treated with antithyroidin gave good results.—M. B. G.

Deductions from 6700 goiter operations. Lahey, F. H., New England J. Med. **200**: 909. 1929.

Based upon vessel ingrowth as a criterion, the incidence of malignancy in a group of 1484 cases of adenomatous goiter was six per cent. Adenomata of the thyroid frequently produce definite changes in the position of the trachea, as is shown by illustrations in the article. The pre-operative employment of iodine has practically eliminated preliminary pole ligation. The patient (954) operative mortality rate in all types of goitre was 0.6 per cent during the year of 1927, and 0.28 per cent in the year 1928 (1068 patients). The dangers of thyroid crises are stressed and measures to avert the occurrence of the condition suggested. There are practically no thyro-cardiacs in which the decompensation is due to a super-imposed thyroidism, that are not operable. Subtotal thyroidectomy, in thyroidism associated with pulmonary tuberculosis, or with diabetes, markedly assists in controlling the associated condition. The necessity of finding at the time of operation any parathyroid glands accidentally removed, and immediately grafting them into a sterno-mastoid muscle, is stressed and experimental indication of its efficacy submitted.—J. C. D.

Clinical investigations into the basal metabolism in diseases of the thyroid gland. Moller, E., Supplementerne XXI to Acta med. Scandinav. pp. 219. 1927.

In 70 cases of typical Graves' disease and 19 cases of the same disease in more or less atypical forms an exhaustive clinical analysis, including numerous basal metabolism determinations with Krogh's method, has been made. It was found that 7 out of 70 patients with typical Graves' disease had a basal metabolic rate within the normal limits. The author concludes that the demonstration of an increase in the basal metabolism is not essential for the diagnosis of Graves' disease. Treatment with rest and overfeeding in most cases caused the basal metabolic rate to decrease 10-20 per cent in 2 to 4 weeks. The effect of x-ray treatment was investigated in 33 cases. Good therapeutic effect was probably present in at least half of these. It was found that, as a rule, the subjective symptoms decreased earlier and more rapidly than the basal metabolic rate. Twenty-three patients with hypothyroidism (18 of which had myxedema) were examined in a corresponding manner. All of these had a decreased basal metabolism. The effect of thyroid treatment was investigated in 19 cases. Whole gland preparations, biologically standardized by the method of Jensen, were used. The increase in basal metabolic rate per unit of dose and per kgm. body weight was calculated. The use did not begin until after 2-3 days and did not reach its maximum for 2-8 weeks.—Author's Abst.

The intracutaneous salt-solution test in thyrotoxicosis. Mora, J. M., Am. J. M. Sc. **177**: 222. 1928.

The intracutaneous salt solution test was studied in 42 cases of thyrotoxicosis, before and after operation. There was a definite decrease in the disappearance time of the wheal preoperatively. After operation, with the return to normal of the basal metabolic rate and the patient's general condition, the disappearance time also became normal. In a general way, the greater the toxemia, the less time was required for the wheal to disappear. The disappearance time of the intradermally injected saline solution paralleled the basal metabolic rate as an index of the severity of the thyrotoxicosis. The literature pertaining to this test is reviewed.—Author's Summary.

The use of iodin in the treatment of goiter. Mosser, W. B., Pennsylvania M. J. **32**: 416. 1929.

The author states that the indications for the use of iodine are: As a prophylaxis for endemic goiter; as an prophylaxis for fetal goiter; as a form of treatment of adolescent goiter; when guardedly used as a form of treatment for colloid goiter, and as a preparatory measure in the surgical treatment of toxic goiter. The drug is contraindicated: in all patients with non-toxic adenomatous goiters; in any patient in whom the goiter has persisted beyond the age of thirty, and as a form of medical treatment of toxic goiter.—I. B.

Inanition and glycogen in thyroidectomized dogs (Inanition et glycogène chez les Chiens thyroïdectomisés). Nitzescu, I. I. and Marie Benetato, Compt. rend. Soc. de biol. **99**: 896. 1928.

Thyroidectomized and control dogs were starved and deprived of water. The controls could live only 20 days, while the operated animals were killed after a month. The amount of glycogen in the liver and in the muscles was greater in the thyroidectomized animals.—J. C. D.

Effect of chlorophyll and thyroxin on the sensitiveness of the organism to reduced oxygen tension (Action de la chlorophylle et de la thyroxine sur la sensibilité de l'organisme a l'égard d'une raréfaction de l'oxygène). Rydin, deH., Compt. rend. Soc. de biol. **99**: 1685. 1928.

Rats injected with thyroxin are less resistant when placed under a bell jar from which the air is withdrawn than are controls or chlorophyll injected animals.—J. C. D.

Effect of chlorophyll and thyroxin on body weight (Action de la chlorophylle et de la thyroxine sur le poids du corps). Rydin, deH., Compt. rend. Soc. de biol. **99**: 1687. 1928.

Thyroxin produces a cessation of growth and actual loss in body weight when injected into rats.—J. C. D.

The experimental production of hoariness and alopecia areata in the rabbit by intensive and prolonged hyperthyroidization (La realization and experimentale de la canitie et de l'alopecie en plaques par l'hyperthyroidisation intensive et prolongee chez le lapin.) Sainton, P. and P. Veran, Presse méd. **36**: 905. 1928.

By prolonged treatment with thyroid the hair coat of rabbits was changed from intense black to reddish black. Blanched areas next appeared, then temporary alopecia and finally the return of mixed black and white hairs.

—H. B. Torrey.

The response of chronic nephrosis to parathyroid and thyroid medication. Lewis, D. S. and W. de M. Scriver, Ann. Clin. Med. **2**: 66. 1928.

Eppinger and Epstein both believe that this condition is due to an endocrine insufficiency, and the latter puts forward a new name, "diabetes albu-

minurica." The symptoms of endocrine origin are a lowered basal metabolism and a marked increase in cholesterol content of the blood. Response to thyroid and parathyroid therapy gives strong evidence of endocrine causation. In 5 of 7 cases reported there was a thyroid insufficiency, with a marked tolerance for thyroid extract. One case responded to parathyroid extract (Collip) by injection after thyroid extract had been tried without success. The mode of action of the parathyroid is uncertain.—M. B. G.

Endemic goiter in California. Searls, H. H., and P. Sharp, California & West. Med. **30**: 231. 1929.

At the University of California Hospital there have been 2289 patients treated for goiter up to January 1st, 1928, and of these 1351 were of the endemic types. No case was accepted for this study where there was any doubt as to the residence at the time of development of the goiter. Maps were drawn showing a goiter belt which runs northward from Monterey County along the coast to Del Norte, then across the northern end of the state, and thence southward, with the highest incidence of all along the western slope of the Sierra Nevada. The view that endemic goiter is a direct result of iodine deficiency is given considerable support by these maps. It was found that the endemic foci lie in the mountainous regions of the northern part of the state. Here the precipitation is very heavy, and for the most part the drinking water travels but a short distance to consumption. Also some of these regions lay under the great ice sheet during the glacial period and have had the iodine washed out of their soil by the large amount of water liberated by the melting ice at the end of that time. The high incidence in the Santa Clara valley may not be accounted for by these causes. The water supply here has only recently been chiefly from wells. Wells in various parts of the world have been notorious in the development of goiter. The possibility that McCarrison's theory (on an infectious basis) explains the focus in the Santa Clara Valley, as it would seem to have in India, must be considered.—I. B.

The tachycardias. Shookhoff, C., M. Clin. North America, **2**: 941. 1928.

This is an excellent resumé of the various forms of heart hurry, with mention of tachycardia in relation to endocrine disturbances. Tachycardias in endocrine secretory disturbances are common. In thyrotoxicosis, it is presumed that the increased or altered thyroid secretion caused an increased sensitization of the sympathetic system to the adrenalin already present in the blood. In the later stages of thyrotoxicosis, the tachycardia may be due to myocardial degeneration. Cannon and Smith believe that the thyroid secretion has a direct effect upon the heart muscle itself. The tachycardias of the menopause and those following castration are also of this type.—I. B.

Radiation therapy in hyperthyroidism. Soiland, A., W. E. Costolow and O. N. Meland, California & Western Med. **27**: 789. 1927.

A careful review of the literature on the surgical management of hyperthyroidism reveals the fact that this form of treatment is by no means without danger, and by no means infallibly curative. Recurrence of symptoms after operation, total lack of benefit post-operatively, and other negative results are encountered. Moreover, the operative mortality rate in clinics is probably 12 to 15 per cent. Treatment of hyperthyroidism by radiation compares favorably with results obtained by surgery. Selection of patients is a prerequisite. Radiation is especially advocated in cases of so-called exophthalmic goiter, and in pure hyperthyroidism. Radiation is not associated with a mortality rate, and is better controlled than is surgery. In post-operative hyperthyroidism, again, radiation is also indicated. The frequency of the persistence of toxicity is due to thymic involvement, which is easily controlled by x-ray. There are no logical contraindications to this form of treatment, if administered by one trained in the work. Myxedema is guarded against by basal metabolic observation during treatment.—I. B.